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Educational Paper

LLL 44 – Module 3: Micronutrients in Chronic disease

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SUMMARY

Micronutrients (MN), i.e. trace elements and vitamins, are essential organic molecules, which are required in the diet in relatively small amounts in any form of nutrition (oral, enteral, parenteral).

The probability of MN depletion or deficiencies should be considered in all chronic illnesses, especially in those that can interfere with intake, digestion, or intestinal absorption. Low socio-economic status and food deprivation are recognized as the most prevalent reasons for MN deficiencies world-wide. Elderly multimorbid patients with multimodal therapy, as well as patients with long-lasting menu restrictions, are at high risk for both disease related malnutrition as well as multiple MN deficiencies, needing careful specific follow-up. The importance of monitoring MN blood levels along with CRP is essential for optimal care. Drug interactions are also highlighted.

In patients with chronic conditions depending on medical nutrition therapy, the provision of adequate dietary reference intakes (DRI) of MN doses and monitoring of their adequacy belongs to standard of care.

Learning objectives

- To acquire basic knowledge on specific MN deficiencies and related health risks in selected chronic diseases, nutrition related conditions and in patients receiving medical nutrition therapy (MNT)
- To be able to identify and interpret the mechanisms causing the increased MN requirements and deficiencies in selected chronic diseases.
- To know which MNs need to be monitored in chronic diseases, particularly in chronic intestinal failure (CIF)
- To understand the value and limitations of methods to assess MN status, including measuring laboratory values in serum or whole blood

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Key messages

- The probability of MN depletion or deficiencies should be considered in all chronic illnesses, especially in those that can interfere with intake, digestion, or absorption of nutrients.
- MN deficiency may be the sole factor causing a chronic disease (e.g. pernicious anaemia), a risk factor for the development or worsening of a chronic disease (e.g. cirrhosis), the inevitable result of a chronic disease (e.g. chronic intestinal failure) or consequence of a treatment modality (e.g. bariatric surgery).
- Elderly multimorbid patients with multimodal therapy, as well as young patients with long-lasting menu restrictions or compromised absorption, are at high risk for both disease related malnutrition (DRM) as well as multiple MN deficiencies and therefore need careful nutritional assessment, monitoring, and treatment of the underlying disease and nutrient deficiencies.
- Sarcopenia and frailty are also generally associated with chronic malnutrition and MN deficiencies.
- Monitoring MN blood levels at intervals during follow up of a chronic patient is essential despite it often being complicated by inflammation.
- Considering the low level of evidence in favour of systematic or individual supplementation, only completion of established losses or compromised intake and replenishment of demonstrated deficiencies is recommended.

Abbreviations

CD	Coeliac disease
CIF	Chronic intestinal failure
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
DRI	Dietary reference intakes
DRM	Disease related malnutrition
FEV1	forced expiratory volume in first second
HEN	Home Enteral Nutrition
HPN	Home Parenteral Nutrition
IBD	inflammatory bowel disease
LLL	Life long learning (ESPEN educational program)
MN	Micronutrient
GLP-1	Glucagon-like-peptide-1
PN-DRI	Parenteral nutrition (PN) daily recommended doses
RCT	randomised controlled trial
RYGB	Roux-en-Y gastric bypass
SG	sleeve gastrectomy

1. Introduction

Medical nutrition therapy (MNT) is an essential part in the multidisciplinary management of numerous chronic diseases. Most guidelines focus on the global metabolic and nutritional management of different diseases, leaving a limited place to micronutrients (MNs).

New standards have been set with the ESPEN Micronutrient guidelines regarding the definitions and wording to be used while describing the status of different MNs in disease [1]. The guideline text stresses that the diagnosis of deficiency requires.

1) Evidence of objective loss or intake below needs, AND
2) the presence of clinical signs or symptoms OR blood/plasma concentrations below reference range together with metabolic effects of inadequacy [1].

The MN-guideline also highlights the importance for the simultaneous determination of the inflammatory response intensity, using C-reactive protein (CRP) levels as the most commonly available inflammation status marker. Inflammation is present in most chronic diseases, and complicates the assessment of the MN status: but there are tools and biomarkers to address this difficulty [2].

The present LLL module (44.3) addresses some common chronic diseases and nutrition related conditions for which major MN status alterations have been shown, providing guidance for diagnostics and prescription. Within the broad variety of chronic diseases, this module is far from being comprehensive.

Each paragraph proposes “practical considerations”. The latter do not have the force of recommendations in absence of hard evidence supporting them: they are based on observational studies and practical clinical expertise of the authors (all being members of the ESPEN MN-special interest group).

2. General aspects of MNs in chronic diseases

The probability of MN depletion or deficiencies should be considered in all chronic illnesses, especially in those that can interfere with intake, digestion, or absorption of nutrients [1,3,4]. MN deficiencies significantly contribute to the increased rates of global morbidity and mortality. If undiagnosed or untreated, MN deficiency can worsen disease symptoms and related malnutrition, also sarcopenia and the prognosis and quality of life.

MN deficiency may be the factor causing a chronic disease (e.g. pernicious anaemia), a risk factor for the development or worsening of a chronic disease (e.g. cirrhosis), the inevitable result of a chronic disease (e.g. chronic intestinal failure) or consequence of a treatment modality (e.g. bariatric surgery).

The causes of MN deficiencies can appear unrelated to the chronic disease, precede the disease or worsen in the presence of the disease or its exacerbation. The causes can be corrected or established with the treatment of the disease, or be ongoing, or they can appear only years after diagnosing or treating a chronic disease, which makes screening of clinical signs and laboratory monitoring of MN deficiencies essential.

2.1. Risk factors: common and patient specific

The risk-factors for and causes of MN deficiencies are similar in chronic diseases and should be assessed concomitantly. Chronic disease may influence the MN needs or losses, availability, quantity, or quality of food intakes. They may also interfere with appetite regulation, food digestion and MN absorption. The MN deficiency risk in chronic diseases varies depending on the patient (age, sex, race, income, appetite, lifestyle, etc), diet (type, menu quality, restrictions, etc), disease type (malabsorptive, metabolic, genetic, progressive, fluctuating, etc), disease duration (months, years, decades) and treatment modalities (dietetic, medical, surgical, radio-, chemotherapy etc). Geographic location also influences the deficiency risks of patients with variations of soil MN content and thus

food MN density, standard menus and food fortification practices, and local treatment and monitoring standards.

Elderly multimorbid patients with multimodal therapy or chronic intestinal failure patients with an acute infectious exacerbation, as well as patients with long-lasting menu restrictions, are all at high risk for both DRM as well as multiple MN deficiencies and therefore need careful nutritional assessment, monitoring, and treatment of the underlying disease and deficiencies. Young patients with successful dietetic therapy of coeliac disease, or those with restrictive surgical therapy of obesity are also exposed to a life-long risk for MN deficiencies, especially under specific conditions, such as pregnancy or breast-feeding.

2.2. Therapy

Prevention of MN deficiencies in healthy populations has traditionally been accomplished by completion, fortification, and food-based approaches including diversification to reach DRIs [5]. Patients on MNT usually need MN doses superior to DRI, and the new term and standard of PN-DRI has been proposed in the ESPEN guideline for parenteral nutrition [1]. These actions should be part of the general treatment plan and documented in the clinical history, especially in patients with MNT need [6]. Follow-up and timely monitoring should be stated in the nutrition care plan of all patients with deficiency risk from chronic diseases and nutrition related conditions.

3. Nutrition related conditions

3.1. Disease related malnutrition (DRM) & starvation

Low socio-economic status and food deprivation are recognized as the most prevalent reasons for MN deficiency world-wide [7]. However, the true prevalence of MN deficiency with DRM is not well known. There is no clear differentiation between acute and chronic malnutrition, but currently DRM is defined by the presence of etiological and phenotypic criteria established by Global Leadership Initiative on Malnutrition (GLIM) and should be separated from simple starvation [8]. Both, DRM and malnutrition from starvation or food shortage, which also leads to the development of several chronic illnesses, can provoke MN deficiency [7].

In the Global Nutrition Report 2020, it was estimated that one-third of people suffer from at least one form of MN deficiency, which particularly affects children and pregnant women. Most common deficiencies concern iron, vitamin A, iodine, folate, and zinc [7]. Deficits of fat-soluble vitamins, iron, and zinc are observed in protein-energy malnutrition among children. Water-soluble vitamins and other trace elements deficiencies have also been reported with variations related to the region and the malnutrition duration [5].

In simple starvation, specific testing of MN deficiencies has not been recommended [5,7], but empiric administration of vitamins and minerals should routinely be included in nutritional rehabilitation. Additional repletion doses, and if available, laboratory assessment should be provided in case of a specific deficiency suspicion based on clinical symptoms or low intake history.

In cases of DRM or high risk of malnutrition, MN status assessment with laboratory biomarker analysis should be performed to diagnose MN deficiencies and without waiting for laboratory results, provide adequate MN dosages from the beginning of the MNT [1].

Clinical signs of MN deficiency can mimic the symptoms of a chronic disease worsening or exhibiting new symptoms. MN deficiency can lead to common syndromes (e.g. anaemia) and be underdiagnosed and left untreated. Deficiency can also present with non-specific worsening of general well-being or lack of response to treatment [5].

However, acute inflammation [1], often present in chronic diseases during exacerbations, complicates interpretation of laboratory analyses of MNs. Inflammation induces a redistribution of many MNs from the circulation compartment to other organs resulting in low levels for most MNs. Low blood levels therefore do not necessarily indicate deficiency or even depletion. A strong clinical suspicion of deficiency based on symptoms should prompt a test of treatment, as MN deficiency can also be present with normal laboratory values. This was shown in a RCT testing multivitamin B intramuscular supplements in 285 elderly adults in which MN supplementation reduced the methylmalonic acid (MMA) and homocysteine concentrations, reflecting a correction of deficiency despite apparently normal blood levels of B6-B9-B12 [9]: a similar situation has been observed in cirrhotic patients.

All patients on MNT should receive at least DRI amounts. Patients with underlying chronic disease with exacerbations and hospitalized polymorbid patients exclusively on oral diet should receive extra attention- MN repletion should be documented based on clinical assessment of the patient needs and intake. In some cases, estimated daily MN requirements may temporarily exceed DRI to compensate for depleted stores and/or increased utilization [10].

In DRM, or in patients at high risk of malnutrition indicating MNT (either oral, enteral, or parenteral), it should be initiated with the MN replenishment with preferably using an oral complex preparation of minerals and trace elements (if oral route is available) and with dosing providing the DRIs. Also much higher replenishment doses are needed for prevention of refeeding syndrome for vitamin B1 (for at least 3days, but in case of suspected or underlying deficiency or clinical symptoms, the treatment may require up to 2–3 months) [1].

3.1.1. Practical considerations

Chronic illness requires individual assessment of risks and needs, and dosing for prevention and adequate treatment in combination with monitoring of clinical symptoms and laboratory markers of MN deficiencies.

3.2. Sarcopenia & frailty

These conditions are generally associated with chronic malnutrition (or ageing). Across observational studies some findings appear consistent, pointing to a key role for antioxidant nutrients (vitamins C and E, selenium), vitamin D, B vitamins and magnesium [11–13]. Poor MN intake, and low blood MN levels are associated with reduced muscle function [13]. However, the evidence is largely observational and limited to associations with different muscle outcomes, with no convincing intervention trial yet.

3.2.1. Practical considerations

The global malnutrition status should be corrected first, while investigating eventual specific deficits of the above listed MN.

3.3. Obesity and bariatric surgery

The pandemic of obesity leads to significant adverse health effects and costs [14]. Obese patients probably have higher needs as well as lower intakes of MNs with diet but the DRIs for most MNs in obese patients have not been defined [10,15].

Obesity is linked to more than 40 other diseases including type 2 diabetes, heart diseases, stroke, and certain types of cancer, which are some of the leading causes of preventable and premature death as well as debilitating health outcomes of other diseases [10,14,16].

Obese and overweight patients are at risk for any MN deficiencies for multiple reasons [16]. Due to limited dietary intake, higher needs and sequestration in fat mass that associate with reduced circulating levels of fat soluble vitamins such as vitamin D [15]. Obese individuals can also experience reduced sunlight exposure because of low outdoor activity that further contributes to causing vitamin D deficiency [17–19]. Low vitamin D status in obese patients relatively to normal weight subjects has been observed in Europe and USA [15,20].

3.3.1. Treatment modalities

Life-style changes combined with energy restriction, medications reducing food intake or digestion, and restrictive or malabsorptive surgery are the standard of care for obesity. With the development of Glucagon-like-peptide-1 (GLP-1) receptor agonists (Liraglutide and analogs) new therapeutic perspectives have finally become available [21].

Metabolic surgery has become very common in the last decades and appears still the most effective therapy in terms of long-term results and treatment of obesity related disease [22]. The American Society for Metabolic and Bariatric Surgery estimated in 2021 that about 264,000 patients had undergone a bariatric surgery procedure, with a predominance of the sleeve procedures. However, these surgical procedures (restrictive, malabsorptive or combining) provoke macronutrient and MN malabsorption making daily MN complementation (with doses far superior to DRI) and nutritional status monitoring necessary in the patients' management [23].

Obesity surgical treatment contributes to reduce the health risks related to excess bodyfat and even treats some of the established related diseases, e.g. the risk for diabetes mellitus (DM) and reduces the need for DM medication [15,22], the treatment of obesity and DM get combined with the new GLP-1 agonist strategy [21]. Different studies suggest that a 5–10% weight loss through lifestyle intervention may improve outcomes and reduce chronic liver disease progression in patients with obesity and compensated liver cirrhosis [14,16,24]. Strong evidence is lacking on MN requirements to maintain muscle mass and adequate support for increased metabolic activity of liver during weight loss programs.

Different types of surgeries-restrictive, malabsorptive or combining - impact the absorption of nutrients differently. Due to postoperative alterations in the absorption, all procedures induce an iatrogenic risk of MN deficiency. And metabolism of micronutrients. The two most common methods for bariatric surgery today are Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) (see the guidelines [10]). Restrictive methods of surgery e.g. SG particularly affect the absorption of vitamin B_{12} and vitamin D, but malabsorptive procedures, e.g. RYGB have a more profound impact on absorption, including that of fat-soluble vitamins as well as other micronutrients. Monitoring should include: folate, B12, A, D, K, copper, iron, and zinc [25].

The dedicated European, British and US guidelines state with a strong consensus that all patients undergoing bariatric surgery should be monitored for nutritional deficiencies before and after bariatric surgery [10].

3.3.2. Practical considerations

All patients having undergone a bariatric surgery procedure need to take daily MN supplements providing doses much higher than the DRI. Table 1 provides an example of a product available in Europe (no conflict of interest). Monitoring of MN status during the first years is an established standard and needs to be done by the bariatric/operating team. Life-long yearly laboratory follow-up is also probably needed despite life-long replenishment dosing as adherence to the replenishment fails within time. The organisation of long-term follow-up is usually regulated by local guidelines.

The prevention of osteopenia/osteoporosis is a mandatory part of the management of these patients with a daily calcium (1200–1500 mg/d) and vitamin D supplements (75 μg in the below product which is 15 times the DRI) [26,27].

4. Coeliac disease

Coeliac disease (CD) is an autoimmune disorder characterized by immune-mediated mucosal atrophy of the proximal small intestine [28] and subsequent malabsorptive symptoms such as diarrhoea and weight loss [29]. It can also present in overweight and obese subjects [10] and may be diagnosed during childhood, adolescence, or even at old age [30]. Coeliac disease patients are sensitive to the protein gluten, mainly contained in wheat, but also found in barley, and rye [28,29] and the immune response is triggered when after consumption, gluten acts as an antigen and causes an immune response that damages the cells of small intestine, resulting in both macro- and micronutrient malabsorption, especially fat, calcium, vitamin B12, B9 (folate), iron, and other nutrients [29–31].

The estimated prevalence of coeliac disease in Europe is between 1:70 to 1:300 but it is underdiagnosed and often goes unnoticed long before the establishment of diagnosis [10,28,29] and therefore poses a risk of MN deficiency. Unexplained iron deficiency anaemia due to malabsorption is often the only clinical sign leading to further investigation and diagnosis. About 5% of patients diagnosed with iron and/or folate deficiency were found to have histologically confirmed coeliac disease after endoscopy and biopsy in a retrospective study by Howard et al. [31].

The treatment of CD consists of a strict gluten-free diet (GFD) in which grains of wheat, rye and barley should be avoided [10,28,29]. As treatment implies strict life-long dietary restriction, the risk of

Table 1
Example of oral complements designed for post bariatric surgery patients in Europe (WLS Forte®, FitForMe international): the product delivers amounts far higher than DRI, most striking increases being for iron, and vitamins B12 and D.

Vitamins	Quantity	DRI percent	Trace elements	Quantity	DRI percent
Vitamin A	600 μg RE	75%	Chromium	160 μg	400%
Vitamin B1	2,75 mg	250%	**Iron**	**70 mg**	**500%**
Vitamin B2	2 mg	143%	Iodine	150 μg	100%
Niacin (B3)	32 mg NE	200%	Copper	3 mg	300%
Pantothenic acid (B5)	18 mg	300%	Manganese	3 mg	150%
Vitamin B6	0,98 mg	70%	Molybdenum	112,4 μg	225%
Biotin (B8)	100 μg	200%	Selenium	105 μg	191%
Folic acid	600 μg	300%	Zinc	22,5 mg	225%
Vitamin B12	**350 μg**	**14,000%**			
Vitamin C	120 mg	150%			
Vitamin D3	**75 μg**	**1500%**			
Vitamin E	24 mg α-TE	200%			

MN deficiency with a menu that is likely to be low in B vitamins, vitamin D, iron, zinc, magnesium, and fibre [28,30]. Although diet reveals inflammation it is different in-between subjects diagnosed with coeliac disease and therefore is the intake of MNs [32].

4.1. Practical considerations

The cornerstone of management is counselling on adherence to a gluten free diet: patients are encouraged to use fortified foods for calcium and vitamin D, and legumes for magnesium and iron. There is no consensus on which MN should be tested initially or monitored thereafter for adequate prevention in adults, but several MN deficiencies respond to adequate GFD. Some need to be replenished and monitored long-term [10,30].

5. Chronic liver diseases: Cirrhosis & MAFLD

Patients with chronic liver diseases can often develop MN deficiencies, irrespective of disease aetiology, and it has been shown to worsen the prognosis and increase mortality [10,33,34] and worsen with disease progression [34].

Compared to the general population vitamin reserves are decreased in chornic liver disease patients, usually due to hepatic dysfunction, low dietary intake, absorption, and increased catabolism [33]. In addition, malabsorption and maldigestion and use of diuretics can contribute to MN deficiencies. Deficiencies of fat-soluble vitamins are more frequently described [10]. As liver insufficiency results in low levels of serum transport proteins, it can potentially lead to an overestimation of deficiencies of lipid-soluble vitamins with laboratory measuring, therefore needs to be coupled with clinical assessment.

The prevalence of MN deficiencies were reported by laboratory biomarkers in a prospective single-centre study including 125 consecutive patients hospitalized for acute decompensation of cirrhosis, mostly of alcoholic aetiology. The main observed MN depletions concerned vitamin D, vitamin A, vitamin B6, and zinc, affecting a vast majority of patients [34]. Patients with more severe disease by Child-Pugh class- C, had significantly lower levels of vitamins A, and zinc, and higher levels of ferritin and vitamin B12 than those in Child-Pugh class A and B. Patients with a higher stage liver disease (MELD) score had significantly lower levels of vitamins A, E, magnesium, and zinc, and higher levels of ferritin and vitamin B12. Severe hepatic insufficiency correlated with lower levels of zinc, vitamin E and vitamin A, and higher levels of vitamin B12 and ferritin [34].

Other studies have confirmed that vitamin D deficiency is prevalent in cirrhosis (64–92%) irrespective of the aetiology and is not limited to patients with cholestatic disease, increasing with the severity of liver insufficiency, as measured with the Child-Pugh classification [35,36]. Some studies have shown that vitamin D deficiency is associated with liver decompensation, high incidence of infection and increased mortality [34,37].

Also vitamin A deficiency has been related to immune system disorders and to a more severe liver disease course. Deficiencies in vitamin E and K have been associated with reperfusion injury after liver transplantation and neuropathies, and with coagulation disorders [38].

Patients with liver cirrhosis are also predisposed to water-soluble vitamin deficiencies, especially vitamin B1, irrespective of cirrhosis aetiology. Deficiencies of pyridoxine (B6), folate (B9) and cobalamin (B12) are common, mainly due to decreased liver reserves [38]. However, there are currently few high-quality studies on the true prevalence of these deficiencies and the need for supplementation.

As for minerals and trace elements, deficiencies of calcium, magnesium, zinc, and iron in the serum of cirrhotic patients is common finding. Zinc deficiency is frequent in chronic liver diseases, such as chronic hepatitis, metabolic-associated fatty liver disease (MAFLD) and liver cirrhosis. Zinc deficiency compromise the essential urea cycle, among others. In such patients, zinc deficiency generates many types of metabolic abnormalities, including insulin resistance, hepatic steatosis, iron overload and hepatic encephalopathy. However, these metabolic anomalies may be improved with zinc supplements [39].

The important topic of viral hepatitis is not addressed herein, despite several studies demonstrating the potent antiviral activity of zinc *in vivo* and *in vitro*, but the data are still insufficient to support clinical guidance (further reading in Kumar S et al. [40]).

The latest guidelines from the European Association for the Study of the Liver on nutrition in patients with chronic liver disease recognize that there are no specific studies or evidence on the benefit of MN supplementation in patients with cirrhosis [41]. However, they suggest that confirmed deficiencies should be replenished in accordance with the general recommendations for usual clinical practice [10].

6. Intestinal insufficiency and chronic intestinal failure

Both patients with intestinal insufficiency and chronic intestinal failure (CIF) are at risk of MN deficiencies due to absence or limited oral intake, malabsorption, high enteral losses, and increased needs from intestinal rehabilitation and chronic disease. CIF patients can also be at risk of overprovision of certain MNs due to limited availability of MN preparations for home parenteral nutrition (HPN) and altered metabolism. Therefore, regular monitoring as well as IV administration of recommended daily MN doses for PN are needed for all CIF patients. Daily standard and increased needs during PN are provided in the ESPEN-MN guideline [1], in the updated chronic intestinal failure guideline [42], and in Table 2.

The availability of parenteral vitamin and trace element products varies from country to country. The fact that in many countries only multi-trace element preparations with fixed combinations are licensed, and that individual trace element products may not be routinely available, is of concern [43]. This makes the MN dosage challenging to manage in many cases.

The ESPEN guideline for CIF recommends the provision of single MN preparations in addition to daily i/v provision, based on the individual needs of a patient on exclusive and total HPN. For patients on supplemental and partial PN & HPN, the provision of MNs should be maximized through sublingual, oral, enteral, intramuscular, or subcutaneous routes, if possible. Within the same guideline for patients with chronic small intestinal dysmotility, the use of replenishing MN in liquid forms is stressed to prevent specific deficiencies [44].

As clinical symptoms and signs as well as vitamin and trace element laboratory deficiencies may take time to develop, regular monitoring is needed based on the individual clinical situation – in stable patients a six-to-twelve-month interval for assessment is considered sufficient [44], In several risk groups for MN deficiency children, pregnant or lactating women, long-term HPN patients and patients undergoing intestinal rehabilitation (e.g. weaning from HPN-) a more intense monitoring and replenishment program is needed, with no exact timing currently suggested. Decreasing or totally stopping PN infusion reduces MN supplementation through i/V routes with a higher risk for MN deficiencies.

Table 2
ESPEN Recommendations for daily vitamin (A) and trace element (B) intakes, (adapted from the ESPEN guideline on chronic intestinal failure in adults - Update 2023 [42]). For analytical methods please see Berger et al. [2].

A

Vitamin	HPN & long-term PN (all values per day)	Clinical deficiency
Lipo-soluble		
A Retinol	800–1100 mg	night blindness, Bitot spots, xerophthalmia, increased susceptibility to infections
D3 Cholecalciferol	200 IU/5 mg	rickets, osteomalacia, increased susceptibility to infections
E αtocopherol	9–10 mg	neurological symptoms and muscle weakness
K2	150 μg, usually provided by lipid emulsions	bleeding, poor bone development, osteoporosis, and increased cardiovascular disease
Vitamin B family		
B1 Thiamine	2.5 mg	neurological, psychiatric and cardiovascular symptoms, lactic acidosis
B2 Riboflavin	3.6 mg	oral-buccal lesions, seborrheic dermatitis, ocular manifestations, anaemia and marrow aplasia
B3 Niacin	40 mg	Pellagra manifested as diarrhea, dermatitis and dementia
B5 Pantothenic acid	15 mg	neurological and gastrointestinal symptoms
B6 Pyridoxine	4 mg	oral-buccal lesions, seborrheic dermatitis, microcytic anaemia, neurological symptoms
B7 Biotin	60 μg	dermatitis, alopecia, ataxia
B9 Folic acid	400 μg	megaloblastic anaemia, and pancytopenia, oral-buccal lesions, neuropsychiatric manifestations
B12 Cyancobalamin	5 μg	megaloblastic anaemia, and pancytopenia, oral-buccal lesions, neuropsychiatric manifestations
C Ascorbic acid	100–200 mg	Scurvy manifested as petechiae and easy bruising, spongy and purplish gums, dry skin, anaemia, poor wound healing, myalgia and bone pain

B

Trace element	HPN & long-term PN (all values per day)	Clinical deficiency
Chromium	10–15 μg	peripheral neuropathy, weight loss, elevated plasma free fatty acids, and hyperglycemia
Copper	0.3–0.5 mg	microcytic anaemia, neutropenia, osteoporosis, hair de-pigmentation, and myeloneuropathy
Fluoride	0–1 mg	Tooth caries
Iodine	130 μg	Goitre, hypothyroidism, growth and mental retardation (children)
Iron	1.1 mg	Microcytic anaemia, queilitis
Manganese	55 μg	Mn toxicity is a greater concern than deficiency. Mn toxicity produces neurotoxicity and liver complications
Molybdenum	19–25 μg	nausea, rapid breathing and heart rate, vision problems, coma
Selenium	60–100 μg	cardiac and skeletal muscle myopathy, and skin and nail effects
Zinc	3–5 mg	alopecia, skin rash of face, groins, hands, and feet, growth retardation, delayed sexual development and bone maturation, impaired wound healing and immune function, diarrhea, and blunting of taste and smell

There is probably a difference in the prevalence of MN deficiencies in CIF patients based on the underlying aetiology of the failure as well as geographical region-with differences in guidelines and monitoring practices, but low laboratory values have been reported for vitamins A, D and C levels, less often for vitamin B12 and E, iron, and selenium. Reports on other MN deficiencies are rare, probably because the laboratory measuring methods are not available to many. Pediatric HPN patients and long-term HPN patients in earlier studies were reported to have high prevalence of iron deficiency anaemia, especially in studies conducted in US, where iron was often not included in HPN solutions for stability reasons. The true prevalence of iron deficiency in adequately supplemented HPN and CIF patients is unknown, but as malabsorptive patients are susceptible to iron deficiency and losses, patients should be screened for iron deficiency regularly and replenished in case deficient.

Among other trace elements, selenium deficiency exposes HPN patients to a greater risk of infection in a study conducted in Canada [45]. For HPN patients, a daily selenium dose of 60–100 mcg/d is considered sufficient for most adults, yet might not be enough for all patients.

Long-term PN may also create a potential for MN toxicities: copper (Cu) toxicity has been reported as hepatic Cu accumulation occurs with PN-associated liver dysfunction and cholestasis. Similarly, manganese (Mn) may accumulate in patients with cholestasis. Although some studies indicate that Cu requirements in TPN are 0.3–0.5 mg/d for adults, this amount may have to be decreased in patients with cholestasis and increased in case of excessive prolonged gastrointestinal fluid losses. Differently from most MNs, copper concentrations increase in the context of inflammation, and this needs to be considered when interpreting laboratory values of plasma levels.

7. Inflammatory bowel diseases

Patients with inflammatory bowel disease (IBD) are at risk of malnutrition and MN deficiencies, especially in patients with Crohn's disease (CD) who have active small bowel disease or patients undergoing intestinal resection [46]. Therefore, nutritional support should be part of the treatment of IBD patients to prevent malnutrition and MN deficiency [47]. Decreased intake, malabsorption, or excess losses are the main cause of nutritional deficiencies, although the underpinning mechanisms are not always clearly identified. Increased metabolic demand related to the active inflammatory process may contribute to nutritional deficiencies. Vitamin B1, B6, B12, A, D, E and K, iron, selenium, and zinc deficiencies may develop in case of IBD [1].

In CD patients, especially with repeated small bowel resections, deficiencies of lipid-soluble vitamins have been described. In case of retinol deficiency with associated night blindness regular vitamin A repletion to restore normal eyesight is needed [48]. Evaluation of hepatic retinol storage reveals higher prevalence of vitamin A deficiency in CD patients than when measurement of serum retinol concentrations [49]. In confirmed cases of deficiency the replenishment doses should at least meet the daily recommendations for adults (respectively 700 μg and 990 μg retinol activity equivalents per day for women for men). Mild deficiency can also be treated with Vitamin A/retinol 3300 IU (retinol equivalents) [1]. Vitamin D deficiency has been proposed to hold a part in IBD pathogenesis due to its role in the regulation of the immune

response [50]. Low levels of vitamin K and D contribute to osteoporosis in IBD patients [51].

Also water-soluble vitamin deficiencies have been described: Vitamin B_1 (thiamine) is another vitamin that has been shown to be deficient in IBD patients and is associated with fatigue and neurological findings [52,53]. Plasma levels of pyridoxal phosphate (PLP) which is the biologically active form of vitamin B6 are also decreased in patients with active ulcerative colitis and CD [54]. However, it should be noted that inflammation may reduce the levels of these vitamins and this should be taken in count while interpreting laboratory analyses. CD patients who have had ileal involvement or resection, often predispose to vitamin B12 (cobalamin) deficiency [55]. In patients with compromised cobalamin absorption, the IM route should be used for supplementation. Patients should receive life-long supplements as intramuscular (IM) injections of 1000–2000 μg of cobalamin every 1–3 months.

Iron deficiency is present in a significant portion of IBD patients and causes fatigue and anaemia [56]. Intravenous iron infusions should be the first choice in IBD patients with active disease [57]. Oral iron supplementation can be used in cases of inactive or mild disease presentation. Zinc and selenium deficiencies are also quite common in IBD and associated with more severe disease and adverse clinical outcomes [58,59].

There is a bidirectional relationship between MN deficiency and IBD (e.g. IBD causes MN deficiencies which contribute to IBD course and activity). Treating deficiencies, especially of iron, zinc, and vitamin D, may have a positive impact on the course of IBD.

8. Chronic pulmonary diseases

8.1. Chronic obstructive pulmonary disease (COPD) and asthma

Chronic obstructive pulmonary disease (COPD), an irreversible disease, has become an important cause of morbidity, disability, and mortality worldwide [60]. The role of the nutrition status in chronic respiratory diseases has long been recognized as a modifiable factor and an important predictor of clinical outcome [61,62].

The COPD pathology of includes pulmonary inflammation, oxidants-antioxidants imbalance, and both innate and adaptive immunity alterations with the inflammation triggered by noxious gases (smoke, air pollution) that causes additional oxidative stress [63]. The development of MN deficiencies is explained by an imbalance between increased utilization (systematic inflammation, oxidative stress) and a poor nutritional intake [64].

Numerous studies have been conducted in asthmatic patients. A meta-analysis including 40 studies showed that dietary vitamin A and C intake and blood levels were lower in the severest asthmatic patients, and associated worse clinical evolution [65]. Chronic vitamin C depletion is also identified in COPD patients due to chronic inflammation, and oxidative stress [1]. Studies connecting vitamins C, E, A, alpha and beta-carotene with spirometric values (forced expiratory volume in first second = FEV1) have shown that higher blood levels of vitamin C and E in food frequency questionnaires and in serum were associated with an increase in FEV1 [63].

Vitamin D insufficiency has long been associated with chronic respiratory infections [65] with very low blood levels correlating with the disease severity [63]. Disease exacerbation occurs with blood levels <25 nmol/L. A study including 1544 current and former smokers (981 subjects were Vitamin D sufficient, 563 deficient) showed that deficiency was associated with worse quality of life, increased dyspnoea, decreased exercise tolerance, and increased frequency of severe exacerbations, and higher segmental airway wall thickness on CT-scan [66]. A German cohort including 9548 adults aged 50–75 years followed over 15 years (cutoffs: insufficiency 30–50 nmol/l 25(OH)D, deficiency <30 nmol/l), showed that poor vitamin D status was frequent with prevalences of 44 and 15% for insufficiency and deficiency, respectively. Vitamin D deficiency strongly increased respiratory mortality with adjusted hazard ratios (95% CI) of 2.1 (1.3–3.2) and 3.0 (1.8–5.2) [67]. Overall, in this cohort, 41% of respiratory disease mortality was statistically attributable to vitamin D insufficiency or deficiency.

Associations of COPD and vitamin E (α-tocopherol = AT) has also attracted attention in the NHANES (National Health and Nutrition Examination Survey) data: in 4706 participants, the vitamin E intakes were low, and higher vitamin E intake was significantly negatively associated with COPD [68]. Recent laboratory data confirm the importance of AT with inhibition of the expression of COX2 by negatively regulating the EGFR/MAPK pathway, thereby inhibiting the translocation of phosphorylated STAT3 to the nucleus and relieving COPD [69].

Zinc, as an intracellular signalling molecule, has also been shown to play important role in cell-mediated immune function and oxidative stress and in regulating the oxidant/antioxidant balance in COPD patients [70]. Zinc supplements further inhibit viral replication and attenuates inflammatory cytokine production in cell cultures. There are no convincing clinical trials yet to support supplementation or suggest replenishment doses.

Studies reporting on MN supplementation are very heterogenous regarding design, outcome variables, vitamin combinations and doses, resulting in inconclusive results [63]. Vitamin D supplementation and replenishment is recommended in several countries, as vitamin D affects both pulmonary and extrapulmonary manifestations of COPD as shown by recent reviews [67,71]. Long-term administration of selenium and/or vitamin E (200 μg/d l-selenomethionine and 400 IU/day all rac-α-tocopheryl acetate), have shown modest positive effects in current smokers with an attenuation of the decline in FEF_{25-75} [72]. Vitamin C supplementation (200–500 mg/day) is also recommended with a low level of evidence in the ESPEN guideline [1,65].

A RCT named ATBC [73] from 1994 did cast a shadow on antioxidant supplementation attempts. The study included 29′133 white male smokers from Finland aged 50–69 years, and tested α-tocopherol 50 mg plus beta-carotene 20 mg, or placebo daily for 5–8 years and found total mortality to be 8% higher among the participants who received beta-carotene than among those who did not, primarily because there were more deaths from lung cancer and ischemic heart disease [73]. This outcome raised the question of harm from beta-carotene supplementation but the post hoc investigation of this study showed that higher serum α-tocopherol status were associated with lower lung cancer risk [74]. But weather the relatively low dose of retinol (about twice DRI) was really responsible for the difference in mortality in this study, remains uncertain.

8.1.1. Practical consideration

In absence of any strong recommendation, the adequacy of MN intakes of COPD patients should be verified with a special focus on vitamin D, C and E with doses modestly above DRI.

8.2. Cystic fibrosis (Mucoviscidosis)

Cystic fibrosis (CF) is a genetic disorder that affects mainly the lungs, but also pancreas, liver, intestines and kidney. The respiratory symptoms and complications dominate the clinical picture, but the involvement of the abdominal organs usually requires medical nutrition therapy. Nutritional interventions include oral/enteral nutrition replenishment, enteric-coated pancreatic enzymes, and water-miscible CF-specific vitamin replenishment [21].

Deficiencies in iron, zinc and fat-soluble vitamins A, D, E, and K (attributable to fat malabsorption) are commonly reported in CF [21].

The nutritional management and monitoring of CF patients is well defined [75]. The prescription includes high fat, high energy diet, combined with pancreatic enzymes to reduce malabsorption, with special supplementation of fat-soluble vitamins (see dedicated guideline [76]). Nutrition education and behavioural counselling for patients with CF and their families is part of the treatment [76].

9. Chronic renal failure

Kidney disease is rising worldwide, and nomenclature has long been imprecise [77]. The text hereafter applies use the KDIGO definition and classification of chronic kidney disease (CKD), ranges from mild to advanced (5 stages) [77]. CKD increases the likelihood of experiencing either a deficiency or an excessive amount of various MNs. Micronutrient deficiency in CKD may develop due to specificity in dietary recommendations, comorbidities, concomitant medication, impaired intestinal absorption, changed metabolism, and excessive loss in urine or dialysate but clear mechanistic understanding remains scarce [78]. As a result, the existing guidelines and recommendations are predominantly derived from expert opinions or low-quality evidence.

Recent evidence has indicated that inadequate levels of MNs might contribute to chronic complications like cardiovascular disease, inflammatory conditions, or cancer. Therefore, many complications related to chronic kidney disease may stem from imbalances in the MN availability. The potential outcomes of MN deficiency may consist of premature death, the development of atherosclerosis, inflammation, oxidative stress, anaemia, polyneuropathy, encephalopathy, reduced strength and fragility, muscle cramps, bone disease, depression, and insomnia. The likelihood of experiencing deficiency in MNs also increases with ageing [79].

The dedicated ESPEN guideline recommends monitoring of trace elements (special attention to copper, selenium, and zinc) and vitamins (special attention to vitamin C, folate, and thiamine) [80]. These recommendations are mainly based on observational studies showing low blood levels of these MNs in patients on hemodialysis [81,82]. A Canadian RCT testing complements of Se 75 mcg, Zn 50 mg and Vitamin E 250 IU per day added to the standard vitamin B and C complements showed that these doses were insufficient to correct the low blood levels [83,84].

Monitoring MN blood levels at intervals during follow up of CRF patients is essential despite it being complicated by haemodilution, inflammation, fasting, or renal replacement therapy [78].

9.1. Practical considerations

The current ESPEN recommendation states that the losses of selenium and other MNs in the effluent fluid should be replaced, guided whenever possible by laboratory analyses of blood levels [80], and that the doses required are superior to the PN-recommended intakes [1].

10. Weaning from home EN/PN

Weaning from PN requires close monitoring by an experienced team and provision of all adequate nutritional needs, especially in children [44]. A retrospective review of data from 178 children with IF reported occurrence of MN deficiencies during the PN to full enteral nutrition transition. Iron was the most commonly identified

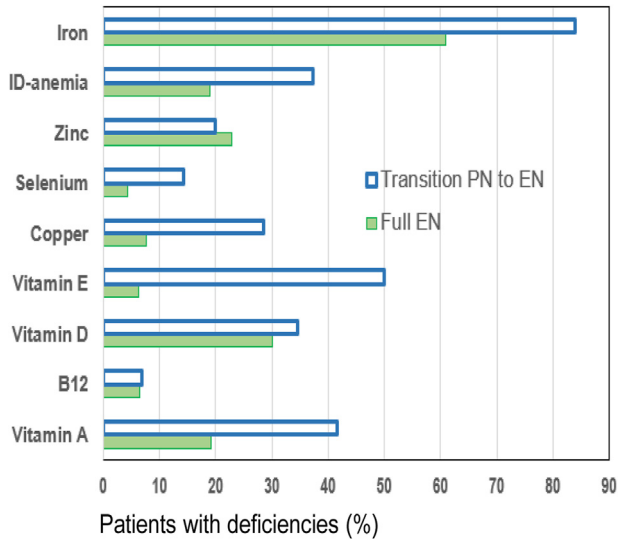

Fig. 1. Prevalence of MN deficiencies in 178 paediatric patients transitioning from prolonged PN to full enteral nutrition. During transition 42.5% of patients had at least one vitamin deficiency, 25% had at least one mineral deficiency, and 27.5% had multiple MN deficiencies. Most common MN deficiencies were of iron, copper, and fat-soluble vitamins during both periods (adapted from Ubesie et al. [85]).

MN deficiency both during (83.9%) and after (61%) successful transition to full EN, with a significant reduction in the percentage of patients with iron deficiency between these 2 periods ($P = 0.003$) [85]. To a lesser extent, deficiency of lipid soluble vitamins was also reported (Fig. 1). No such data are yet available in adults.

The Home EN (HEN) guideline [86] recommends that "HEN should be terminated when the desired weight has been reached and the patient's oral intake matches his/her maintenance needs."

Although studies are insufficient to provide exact recommendations for MN monitoring during HEN or its weaning, a meta-analyses of 31 studies ($n = 744$) reports MN deficiencies in HEN patients for copper, zinc, selenium, beta-carotene, and vitamins A, D and E. Physical and haematological manifestations of deficiency were observed only in case of copper, zinc and selenium deficiencies [87]. The authors conclude that the deficiency risk should be acknowledged especially for those who present a higher risk during low volume feeding, or in patients receiving jejunal feeding (risk of copper deficiency), and in patients commencing EN in a nutritionally depleted state.

11. Drugs-MN interactions

Several widely used drugs can lead to interactions with MN absorption, utilization, or excretion, causing deficiencies of specific vitamins and minerals [1,88–91]. A particularly high risk for the individual arises when predisposing comorbidities or risk factors coexist, for example the combined use of metformin and proton pump inhibitors (PPI) in a patient with previous bariatric surgery or on a vegan diet (Table 3) [92]. Awareness of these drug-MN interactions and their clinical consequences is of great importance for their management, usually with a combined approach of identifying patients at risk and using MN monitoring/adding supplementation in often higher doses than standard DRIs. Some of these interactions include:

Proton Pump Inhibitors (PPIs): Very commonly used drugs, their long-term use can reduce the absorption of essential nutrients such as vitamin B12, magnesium, calcium, and iron [93].

Table 3
Drugs impacting the different MNs and electrolytes (adapted from Laight [92]).

Vitamins	
Vitamin A	Bile acid sequestrants
Vitamin B1 – Thiamin	Antibiotics, diuretics
Vitamin B2 – Riboflavin	Antibiotics, estrogens
Vitamin B3 – Niacin	Antibiotics
Vitamin B 6 – Pyridoxin	Antibiotics, anticonvulsants, diuretics, estrogens, isoniazide
Vitamin B 7 – Biotin	Antibiotics, anticonvulsants
Vitamin B9 – Folate and folic acid	Antacids, anticonvulsants, bile acid sequestrants, estrogens, folic acid, metformin, methotrexate, nonsteroidal antirheumatic drugs, opioids
Vitamin B12 – Cobalamin	Antacids, antibiotics, anticonvulsants, estrogens, H2-receptor antagonists, metformin, methotrexate, PPIs
Vitamin C	Antacids, diuretics, estrogens, PPIs, opioids
Vitamin D	Anticonvulsants, antiretroviral treatments, bile acid sequestrants, corticosteroids, statins
Vitamin E	Bile acid sequestrants
Vitamin K	Antibiotics, vitamin K dependent anticoagulants, bile acid sequestrants, opioids
Trace elements	
Iron	Antacids, bile acid sequestrants, nonsteroidal antirheumatic drugs, opioids, PPIs
Selenium	Diuretics
Zinc	Diuretics, estrogens, RAAS inhibitors
Minerals	
Calcium	Antacids, anticonvulsants, corticosteroids, diuretics, PPIs
Magnesium	Antacids, diuretics, estrogens, metformin, PPI
Potassium	Diuretics, mineralocorticoids, RAAS inhibitors
Sodium	Diuretics, mineralocorticoids

Antacids: Over-the-counter antacids containing aluminium can interfere with the absorption of phosphorus and calcium, potentially leading to deficiencies of these minerals over time.

Antibiotics: Some antibiotics can impair the function of beneficial gut bacteria, potentially affecting the production and absorption of vitamin K and some B vitamins.

Metformin: Metformin can reduce the absorption of vitamin B12 and increase the risk for vitamin B12 deficiency [94].

Antihypertensives: ACE inhibitors/angiotensin II receptor antagonists have been associated with zinc depletion and an increased risk for hyperkalaemia.

Corticosteroids: Long-term use of corticosteroids like prednisone can reduce calcium absorption and reduce vitamin D production.

Methotrexate: Interferes with folic acid metabolism, leading to folate deficiency.

Anticonvulsants: Some older anticonvulsants (i.e. carbamazepine, phenytoin, valproic acid) interfere with vitamin D, folate, and calcium metabolism. Valproate can also interact with carnitine metabolism.

Statins: Interact with vitamin D metabolism and coenzyme Q10 synthesis.

Cholestyramine/Colestipol: Can bind to fat-soluble vitamins (A, D, E, K) in the digestive tract, reducing their absorption.

Diuretics: Can lead to potassium, magnesium and thiamine deficiencies [42,95].

Anticoagulants: Patients on anti-vitamin K medication, such as warfarin, need to be careful with sudden changes in vitamin K intake.

12. Conclusion

In patients with chronic conditions depending on medical nutrition therapy, MNs require special consideration as multiple events may compromise their status. In all chronic diseases complicated with malnutrition there is a risk of MN deficiency. The first step of management of chronic diseases and nutrition related conditions is ensuring that the patient is provided the DRI of al MNs, the regular laboratory analyses of blood levels and monitoring of clinical signs should follow to detect development of inadequacy in provision and replenish deficiencies according to individual optimisation of MN provision.

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