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EDITORIAL

Micronutrient deficiency in critical illness: an invisible foe?

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In critical illness, clinical features such as encephalopathy, muscle weakness, peripheral neuropathy, skin and mucosal lesions, and protracted organ dysfunction dominate the clinical picture (Fig. 1) Micronutrient deficiencies—reviewed in this viewpoint article—might contribute to this clinical phenotype and may, moreover, compromise acute outcome.

Preventing refeeding-related morbidity and mortality

Vitamin B1 (thiamine) is a key co-factor in substrate oxidation. Thus, thiamine deficiency affects major constant energy-dependent organs such as the heart (wet beriberi) or the brain (Wernicke's and Korsakoff's syndrome) [1]. Deficiency risk factors (e.g., diuretics, continuous renal replacement therapy (CRRT), and inadequate premorbid intake) are common in the ICU and body stores are low. Low thiamine plasma levels have been reported in ICU, but real-time monitoring is currently impossible. Clinically, thiamine depletion may only manifest itself when feeding is initiated. This "refeeding syndrome" is easily overlooked as it resembles the clinical phenotype of critical illness [1]. Moreover, this syndrome likely involves other biochemical abnormalities beyond thiamine deficiency [2]. In patients who, upon initiation of artificial nutrition, develop a significant decrease in serum phosphate levels and/or hypophosphatemia, temporary caloric restriction dramatically increased survival in a multicenter randomized-controlled trial (RCT) involving more than 400 patients [2], even though phosphate was adequately repleted in both study arms. An observational study confirmed this pattern. Moreover, at-risk patients could not be identified based on ICU-admission characteristics [3]. Even with limited evidence, given the potential lethal consequences, monitoring and supplementing phosphate, restricting early nutrient administration, and providing ample doses of thiamine (> 100 mg/day) appear prudent.

Vitamin C and vitamin D repletion

Vitamin C, an electron donor, plays an important role as antioxidant, and co-factor for multiple enzymes. During critical illness and particularly sepsis, reduced intake and increased oxidation can lower vitamin C levels, leading to free radical excess and, consequently, loss of endothelial nitric oxide synthase function [4]. This notion has inspired the hypothetical concept of high consumption and relative vitamin C deficiency with the implied need to deliver pharmacologic doses (6 g/day) [4]. However, studies so far have been small or partly retrospective and the aggregated results of three RCT's evaluating vitamin C repletion in ICU have not generated conclusive results [5].

The vitamin D receptor impacts gene transcription in many organs and tissues, and its effects stretch far beyond calcium homeostasis and skeletal integrity to the cardiovascular system, immunity, and inflammation [6]. At ICU admission, more than 50% of critically ill patients have low 25-hydroxyvitamin D levels and 24% have very low levels [7]. Such low levels do not recover during ICU stay and are inversely associated with recovery and survival [8]. They have been attributed to lower premorbid intake, reduced renal conversion, lower levels of the circulating binding protein, and reduced hepatic production, exposure to sunlight and enteral intake [7]. Aggregating data from three RCTs did not reveal survival benefit with vitamin D repletion [5]. The VITDAL-RCT

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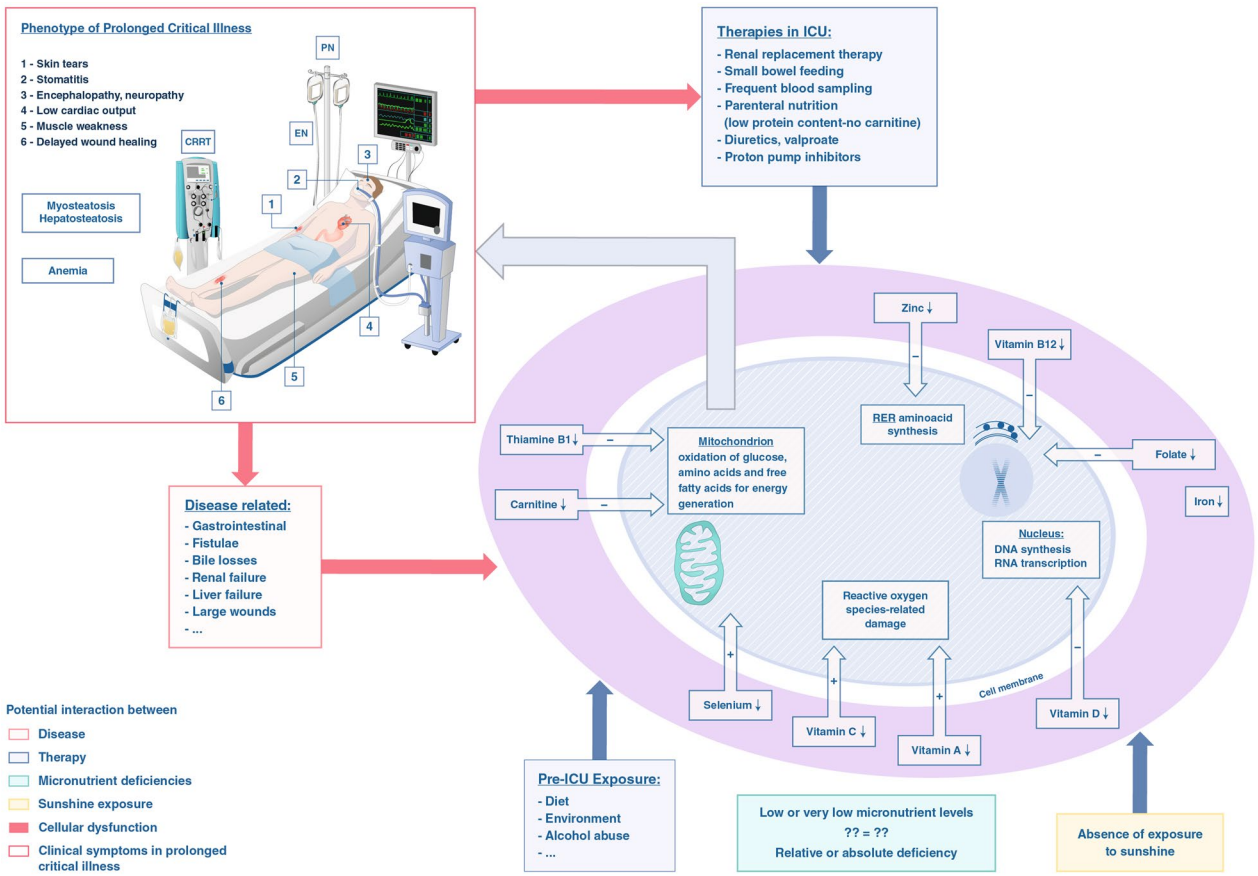

Fig. 1 Visual abstract aggregating potential impact of premorbid exposure, ICU therapies and disease on micronutrient levels, the cellular metabolic role of these micronutrients, and potential contribution of their deficiency to the clinical features of prolonged critical illness (encephalopathy, muscle weakness and neuropathy, stomatitis, skin tears and dermatitis, delayed wound healing, low cardiac output, and recurrent infections). *PN* parenteral nutrition, *EN* enteral nutrition, *CRRT* continuous renal replacement therapy, *RER* rough endoplasmatic reticulum, *DNA* DeoxyriboNucleic acid, *RNA* RiboNucleic acid

generated the hypothesis that correction of very low levels may increase survival [8]. On-going RCT's will provide a better understanding of whether low vitamin C or D levels are morbidity- or mortality-causing deficiencies, epiphenomena, an adaptive response to severe illness, or a combination of any of these (Table 1) [8, 9].

Vitamin B12, folate, zinc, and carnitine

Vitamin B12 supports DNA synthesis and macronutrient metabolism, in particular L-methylmalonyl-CoA and homocysteine pathways [10]. Upper gastric surgery or small bowel feeding and, possibly, proton pump inhibitors may hamper vitamin B12 absorption [10]. Folate, a carbon-transferring co-factor, is also crucial to nucleic and amino acid synthesis [10]. Low levels are common in ICU, especially in the setting of alcoholism, hemolysis, malignancy, drugs like methotrexate and trimethoprim, and CRRT [11]. Clinically, Vitamin B12 or folate deficiency could be easily overlooked as their hallmark, megaloblastic anemia, may not develop in the iron and erythropoietin-deficient ICU context. Plasma levels are unreliable. Unexplained cognitive changes or clinical evidence suggestive of demyelination may thus be the first sign for B12 deficiency [10], a suspicion that can be confirmed by increased homocysteine and methylmalonyl-CoA concentrations. Thrombocytopenia or leukopenia may suggest folate deficiency. Given the difficult clinical and laboratory diagnosis for both deficiencies, prophylactic administration may provide a cost-effective alternative. In a small RCT, parenteral folate at 5 mg/day appeared safe [12].

Table 1 Key multicenter randomized controlled trials of vitamin C and vitamin D in critical illness

NCT number	Country	Number of patients	Condition	Primary outcome	Design
NCT03680274	Canada	800	Sepsis	Mortality or persistent organ dysfunction	Double-blind—high-dose vitamin C
NCT 03509350	USA	2000	Sepsis	Vasopressor and ventilator-free days	Double-blind—high-dose vitamin C + B1 and hydrocortisone
NCT 03333278	ANZ	216	Septic shock	Duration of vasopressor support	Single-blind high-dose vitamin C + B1 and hydrocortisone
NCT 02106975**	USA	170	Septic ALI	SOFA score	Double-blind—high-dose vitamin C
NCT 03389555	USA	200	Sepsis	SOFA score	Double-blind—high-dose vitamin C + B1 and hydrocortisone
NCT 03188796	Austria and Belgium (other European ICU's are in preparation)	2400	ICU patients anticipated to stay > 48 h	Mortality at 28 days	Double-blind—High-dose vitamin D
NCT03096314	USA	1360	Patients planned for admission to the ICU	Landmark mortality on day 90	High-dose vitamin D

Only multicenter studies are included with > 100 patients randomized or expected to be randomized

ANZ Australia and New Zealand

**Only studies currently recruiting or completed

Zinc is a co-factor in DNA synthesis and RNA transcription [13]. Adequate levels depend on precisely regulated intake and excretion [14]. Intake may be inadequate in vegetarians or alcoholics, and may provoke immune dysfunction, hypogonadism, acrodermatitis, and growth disorders [13, 14]. Urinary and cutaneous losses in burns, trauma and sepsis, CRRT, and biliary losses may affect zinc homeostasis [14]. Four studies evaluating repletion in different doses or compared with placebo in non-selected ICU patients found no effect on mortality [5]. High serum copper concentrations or a positive clinical response to empirical treatment may be valuable alternatives to measuring serum zinc concentrations, the latter potentially reflecting redistribution [14, 15].

Carnitine depletion hampers the mitochondrial carnitine/palmitoyl shuttle, causing impaired oxidation of long-chain fatty acids and mitochondrial energetic dysfunction [16]. In patients with prolonged critical illness, liver and kidney dysfunction, reduced amino acid, and vitamin C intake, specific drugs (e.g., valproate) and CRRT may cause deficiency. Unexplained muscle weakness, cardiac failure, or hypertriglyceridemia should trigger clinical suspicion, but uncertainty regarding the ratio of tissue-to-plasma levels complicates confirmation. Interventional trials in ICU have been inconclusive and so far focused on early blood level-unadjusted administration [17].

Conclusion

Our lack of knowledge of micronutrient pathophysiology and requirements during critical illness is striking. Based on the very limited evidence available today, we suggest clinicians to:

1. Prevent refeeding syndrome and, in case it develops, react by restricting caloric intake with slow increase over 5 days, while phosphate is replenished and higher dose (> 100 or 200 mg) thiamine administered in patients at risk of Wernicke's encephalopathy.
2. Systematically consider the possibility of micronutrient deficiency (the "invisible foe") in critically ill patients.
3. Guarantee provision of at least dietary reference intakes of micronutrients in critical illness.
4. Consider additional repletion of vitamin C, vitamin D, B12, folate, zinc, and carnitine in high-risk patients.

Beyond the above principles, several trials of pharmacologic vitamin repletion (esp. vitamin C, thiamine, and vitamin D) are in progress and clinicians should carefully follow the literature for novel developments (Table 1). Moreover, estimates of the potential impact of deficiencies could be improved by concurrent assessment of serum or tissue micronutrient levels in RCTs of other therapies that might affect their levels (Fig. 1). Finally, the cost-effectiveness of targeted

detection–correction versus empirical higher dose administration should be considered.

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Conflicts of interest
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