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Review

Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence

E. Wesselink [a], W.A.C. Koekkoek [b], S. Grefte [c], R.F. Witkamp [a], A.R.H. van Zanten [b, *]

[a] Division of Human Nutrition and Health, Wageningen University, Stippeneng 4, 6708 WE, Wageningen, The Netherlands
[b] Department of Intensive Care Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716, Ede, The Netherlands
[c] Human and Animal Physiology, Wageningen University, De Elst 1, 6708 DW, Wageningen, The Netherlands

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SUMMARY

Persistent physical impairment is frequently encountered after critical illness. Recent data point towards mitochondrial dysfunction as an important determinant of this phenomenon. This narrative review provides a comprehensive overview of the present knowledge of mitochondrial function during and after critical illness and the role and potential therapeutic applications of specific micronutrients to restore mitochondrial function.

Increased lactate levels and decreased mitochondrial ATP-production are common findings during critical illness and considered to be associated with decreased activity of muscle mitochondrial complexes in the electron transfer system.

Adequate nutrient levels are essential for mitochondrial function as several specific micronutrients play crucial roles in energy metabolism and ATP-production. We have addressed the role of B vitamins, ascorbic acid, α-tocopherol, selenium, zinc, coenzyme Q10, caffeine, melatonin, carnitine, nitrate, lipoic acid and taurine in mitochondrial function. B vitamins and lipoic acid are essential in the tricarboxylic acid cycle, while selenium, α-tocopherol, Coenzyme Q10, caffeine, and melatonin are suggested to boost the electron transfer system function. Carnitine is essential for fatty acid beta-oxidation. Selenium is involved in mitochondrial biogenesis. Notwithstanding the documented importance of several nutritional components for optimal mitochondrial function, at present, there are no studies providing directions for optimal requirements during or after critical illness although deficiencies of these specific micronutrients involved in mitochondrial metabolism are common. Considering the interplay between these specific micronutrients, future research should pay more attention to their combined supply to provide guidance for use in clinical practise.

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1. Introduction

Due to improvements in clinical care and technological advancements, the number of patients surviving critical illness continues to rise, albeit often at the expense of health problems later in life [1]. Residual clinical motor and sensory neurologic deficits are extremely common in long-term survivors of critical illness and mortality rates are higher compared to age-matched controls [2,3]. Even five years after discharge from an intensive care unit (ICU), many patients suffer from impaired pulmonary function, muscle weakness and reduced ability to perform vigorous exercise [4,5]. Next to these physical limitations, many survivors complain about social isolation, sexual dysfunction, anxiety, depression and other mental health problems [2,5]. This myriad of symptoms is known as post-intensive care syndrome [6]. As a consequence, ICU survivors are more likely to be readmitted to the hospital and ICU, and demand more home-care compared with non-ICU hospitalized patients [7]. This calls for further research into the aetiology, modulating factors and possible ways for prevention or intervention of this syndrome.

An important cause of physical weakness is the loss of muscle mass and function during critical illness [8]. Interestingly, intracellular signalling patterns associated with increased muscle

* Corresponding author. Department of Intensive Care Medicine, Hospital Medical Director, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, The Netherlands. Fax: +31 318 43 41 16.
E-mail addresses: vera.wesselink@wur.nl (E. Wesselink), koekkoekk@zgv.nl (W.A.C. Koekkoek), sander.grefte@wur.nl (S. Grefte), renger.witkamp@wur.nl (R.F. Witkamp), zantena@zgv.nl (A.R.H. van Zanten).

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Abbreviations

ATP	Adenosinetriphosphate
α-KGDH	Alpha-ketoglutarate dehydrogenase
cAMP	Cyclic adenosinemonophosphate
CoA	Coenzyme A
CoQ10	Coenzyme Q10
DNA	Deoxyribonucleic acid
FAD (H)	Flavin adenine dinucleotide (reduced)
FMN	Flavin mononucleotide
ICU	Intensive Care Unit
LA	Lipoic acid
mtDNA	Mitochondrial deoxyribonucleic acid
NAD (H)	Nicotinamide adenine dinucleotide (reduced)
NFκB	Nuclear factor kappa B
NRF	Nuclear respiratory factor
OXPHOS	Oxidative phosphorylation
PDH	Pyruvate dehydrogenase
PGC-1α	Peroxisome proliferator-activated receptor-gamma coactivator
Se	Selenium
TCA	Tricarboxylic acid
Tfam	Mitochondrial transcription factor A
TQ	α-tocopheryl quinine
RNS	Reactive nitrogen species
ROS	Reactive oxygen species

breakdown and decreased muscle synthesis are upregulated [7,9]. Loss of muscle mass and function has been shown to be more pronounced in patients with multi-organ failure compared with patients with single organ failure, indicating that it is related to disease severity.

Therapeutic interventions aiming to restore or prevent loss of muscle mass and function include exercise and increase of protein intake during and shortly after critical illness. However, conflicting results regarding their benefits have been published [10–13].

Recently, the attention has shifted towards persistent mitochondrial dysfunction as a critical factor [14], since the majority of patients show a reduced ability to produce ATP, which is called bio-energetic failure [15] (Fig. 1). Interestingly, restoring mitochondrial bio-energetic functions has been shown to increase muscle force in septic mice [16], and up-regulation of genes involved in mitochondrial biogenesis was associated with survival [17]. It is well established that for optimal function mitochondria require a range of co-factors, including many micronutrients. To further explore this, we aimed to 1) assess the scientific literature on mitochondrial dysfunction during and after critical illness, and 2) describe potential roles of specific micro-nutritional components in preventing or restoring mitochondrial damage resulting from critical illness.

2. Mitochondrial bio-energetics

The primary function of mitochondria is to supply cellular energy by producing adenosine triphosphate (ATP) (Fig. 2).

Apart from energy metabolism, mitochondria also play essential roles in cell signalling, cellular differentiation, and cell death, as well as control of the cell cycle and cell growth [18].

Bio-energetic failure of skeletal muscle is suggested to be associated with ICU-acquired weakness [14]. The OXPHOS system, essential for ATP production, has been shown to be affected in muscles of critically ill patients [15,19–22] (summarized in Table 1). ATP production is significantly decreased during critical illness [15,19,21], and even more profoundly in non-survivors [19]. Accordingly, the activity of several complexes involved (Fig. 2) has also been found to be decreased. Specifically, the activity of complex I [21,22], III [15], and IV [15,21,22] expressed per mg muscle wet weight was significantly decreased in critically ill patients compared with controls. The activity of complexes I [19,21] was even more decreased in non-survivors. Contrary to these results, when normalized on citrate synthase activity, which is often used as a marker for mitochondrial content, the activities of complex I, and IV did not differ in critically ill patients compared to controls [15,20,21]. Also increased activity of complex II and III in critically ill patients [15] and of complex IV in non-survivors compared with survivors was reported [21]. Caution should be taken when data is normalized on citrate synthase, because its activity itself may change as a consequence of disease or treatment [15,20]. Moreover, citrate synthase activity is regulated by its end product, ATP, which has been shown to be reduced in critical illness, in particular in sepsis [23]. Although data on the course of mitochondrial function during critical illness are lacking, results of recent studies strongly suggest that mitochondrial bio-energetic function is impaired during and after critical illness. Interestingly, 2 h after a human endotoxin challenge, in order to mimic sepsis, complex I and citrate synthase activity increased compared to controls suggesting increased mitochondrial functioning. Why and when mitochondrial function eventually decreases remains to be answered. Moreover, in survivors, mitochondrial regeneration follows damage [17,19,21,24], underlining that proper mitochondrial functioning is essential for survival.

2.1. Substrate oxidation during critical illness

High plasma levels of lactate and free fatty acids, hyperglycaemia and hypertriglyceridemia are indicators of major changes in intermediary metabolism in critically ill patients [25]. Under normal physiological conditions, an increase in glucose concentration stimulates insulin secretion, which in turn suppresses lipolysis and stimulates glucose uptake in different tissues, including muscle.

However, during critical illness, this normal inverse relationship between fatty acid and glucose availability is disturbed. The stress response stimulates a more general energy mobilization involving both glucose and fatty acids simultaneously. During critical illness, the usual suppressive effects of ingested carbohydrates on hepatic glucose output are diminished, leading to hyperglycaemia [26]. In addition, excessive lipolysis occurs leading to high plasma free fatty acids and increased concentrations of VLDL-TG, which in turn causes an increased hepatic triglyceride production [25]. Under normal conditions, increased levels of free fatty acids would stimulate beta-oxidation. However, this response is inhibited during critical disease as the increased rate of glycolysis inhibits carnitine acyltransferase I via malonyl Co-A [25,27].

Interestingly, this balance between energy substrates is not only disturbed during the critical stages of illness but may continue during the recovery period. For example, a recent study found that patients surviving severe burn injury showed no capacity to utilize fat for energy in the muscles months after ICU discharge, limiting exercise performance to only a few minutes [1].

2.2. Factors involved in mitochondrial damage

Originally, hypoxia was considered the leading cause of the decreased ATP production seen in critically ill patients [28].

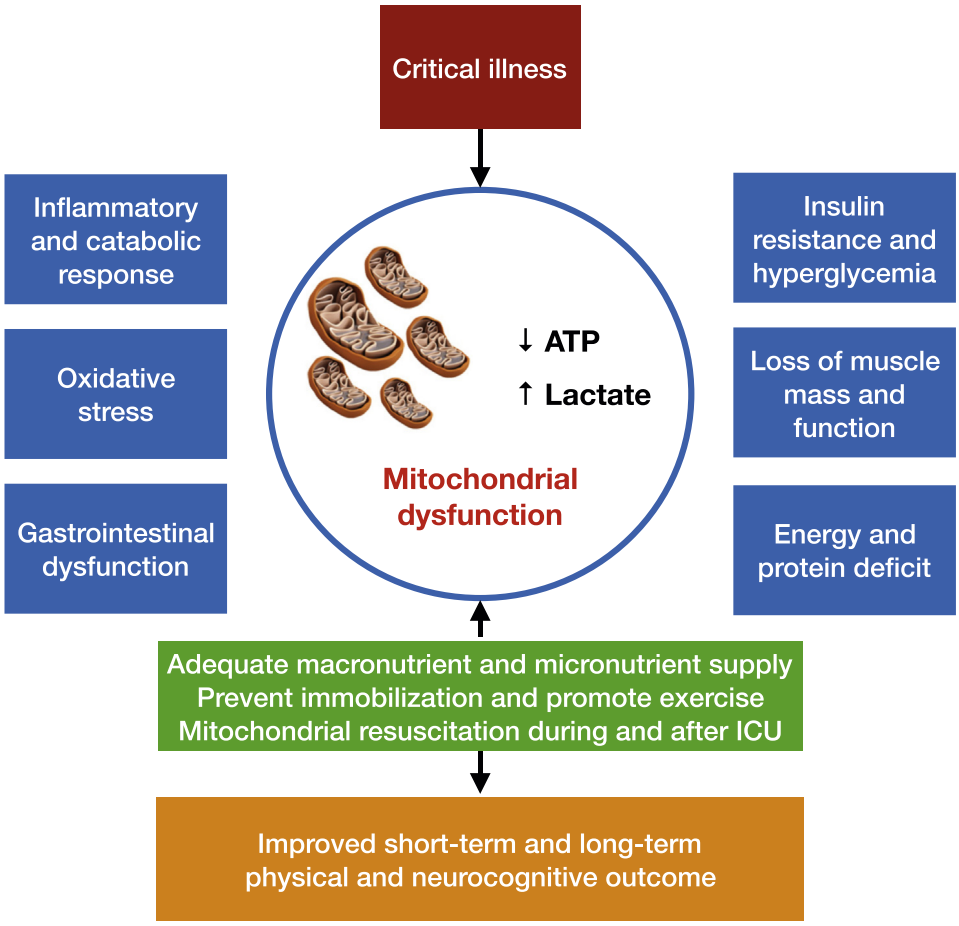

Fig. 1. Factors affecting mitochondrial function during and after critical illness. Mitochondrial function is essential to survive critical illness. Several factors are associated with mitochondrial dysfunction. Mitochondrial dysfunction is associated with decreased energy production reflected by lower ATP availability and increased lactate levels. Adequate nutrition during and after critical illness may improve mitochondrial function and result in better long-term physical and neurocognitive outcomes after critical illness. ATP: adenosinetriphosphate; GI-tract: Gastro-intestinal tract.

However, studies in critically ill septic patients finding elevated tissue oxygen levels in combination with decreased oxygen consumption and altered microvascular flow suggest a problem in cellular respiration rather than in oxygen delivery [29]. The fundamental failure in cellular respiration was named 'cytopathic hypoxia' by Fink [28].

An important factor involved in mitochondrial damage is oxidative stress. Under normal physiological conditions mitochondrial reactive oxygen species (ROS) production and detoxification are tightly balanced [30]. A slight shift in this balance can lead to the activation of important cell signalling pathways [30]. However, oxidative stress occurs when the mitochondrial ROS production significantly exceeds the capacity of the cellular antioxidant systems [31]. This can cause irreversible damage to the lipid mitochondrial membrane, enzymes and mtDNA and thereby induce cell damage and death [31]. Oxidative stress-mediated damage to mtDNA can lead to a vicious cycle of ROS production (ROS-induced ROS release) and further mtDNA damage [31], ultimately leading to loss of function of enzymes in the electron transfer system and/or cell death [32]. This is known as the 'mitochondrial catastrophe hypothesis [31].

Oxidative stress in mitochondria probably decreases ATP production by direct inhibitory effects on complexes of the respiratory chain. It has been suggested that complex IV is temporarily inhibited by nitric oxide [33,34], while the inhibition of complex I is more stable and induced by peroxynitrite [34].

Antioxidants and antioxidant enzymes reduce oxidative stress by four mechanisms, thereby limiting damage to mitochondria [35]: (1)scavenging free radicals, (2)sequestration of transition metal ions into complexes, (3)repairing damage molecules and (4) breaking chain reactions initiated by free radicals, as in lipid peroxidation [36]. Dietary deficiencies of protein, selenium, and zinc are associated with cell injury. However, an excess of antioxidants may be harmful as well, and an overload of specific nutrients, such as iron and vitamin C, may lead to increased oxidation and cell injury [35].

In addition to oxidative stress, glucose homeostasis is also crucial for the proper functioning of mitochondria [37]. However, this is beyond the scope of this review.

3. Micronutrients in mitochondrial function

Several vitamins and (trace) minerals are essential for mitochondrial functioning, either by acting as cofactors in energy metabolism and/or by acting as antioxidants. These two functions are linked as the antioxidant function may prevent damage to enzymes involved in energy metabolism, thereby limiting the reduction in energy production [31]. The role of antioxidant vitamins and trace elements in critically ill patients has recently been investigated by our research group [38].

The focus of the current review is to address the potential role of various nutrients, vitamins and trace elements in mitochondrial

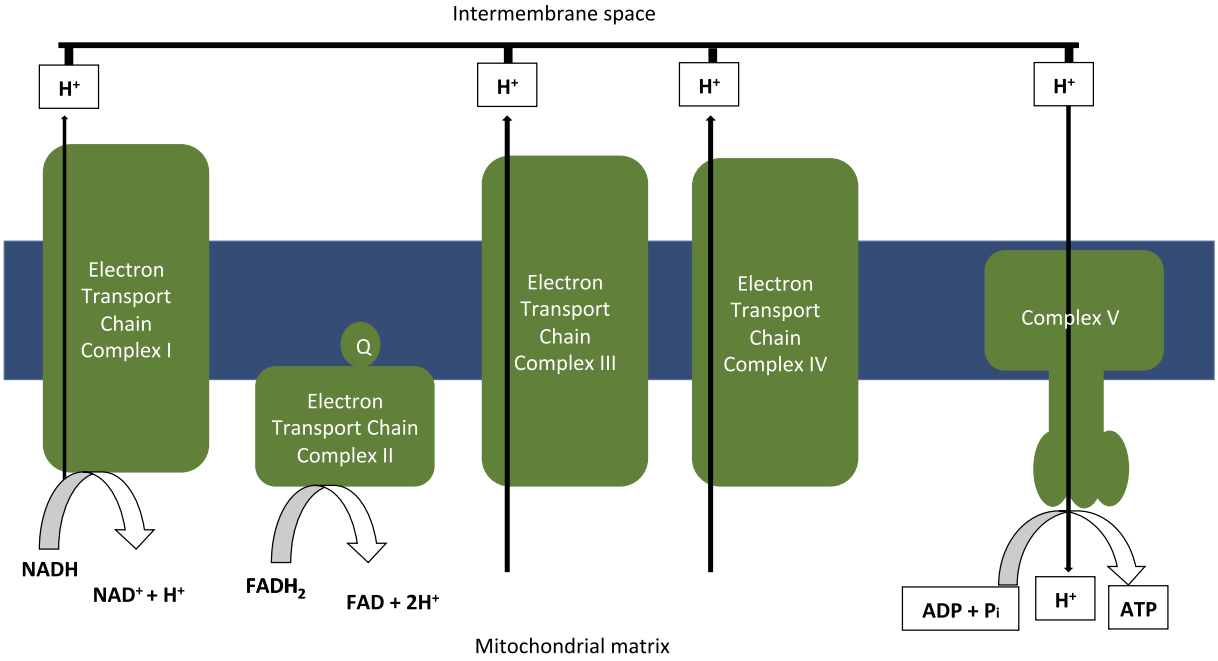

Fig. 2. Mitochondrial energy production. The oxidative phosphorylation (OXPHOS) system consists of five mitochondrial complexes and provides cellular energy by generating adenosinetriphospate (ATP) from adenosinediphosphate (ADP). The electron transport chain consists of the first four mitochondrial complexes. NADH and FADH2 are used as electron donors by the first and second complex. Mitochondria depend on the availability of reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2), which are generated during the utilization of glucose, fatty acids and, to a lesser extent, amino acids [14]. The energy released during the electron transfer through the electron transport chain is used to pump protons (H+) in the mitochondrial matrix over the inner mitochondrial membrane into the intermembrane space. This process generates a proton gradient across this membrane. The energy stored in this proton gradient is used by THE FOF1-ATPase (complex V), which together with the electron transport chain forms the OXPHOS system, to generate ATP from ADP and inorganic phosphate [14].

performance. It should be noted that although these specific micronutrients play important roles in mitochondrial function, the relevance in critical illness is speculative since only very few studies are conducted in critically ill patients. The next sections will elaborate on the potential roles of B vitamins, ascorbic acid, tocopherol, selenium, zinc, coenzyme Q10, caffeine, melatonin, carnitine, taurine, lipoic acids, nitrate and resveratrol, all food components found to be involved in mitochondrial function.

Most important properties, problems arising with deficiencies, recommended dietary allowance and when available guidelines of described nutritional components are summarized in Table 2. Figure 3 depicts an overview of relevant bioactive substances within the mitochondria with respect to energy metabolism and the respiratory chain.

3.1. B vitamins

3.1.1. Thiamine (vitamin B1)

Thiamine deficiency is common in critically ill patients (10–30%) [43,83–88]. Low serum thiamine levels in critically ill patients were found to be associated with worse outcome and increased mortality [86,89]. However, a recent prospective study in 108 patients did not find an association between serum thiamine levels and mortality [90]. Although Marik and co-workers did not study mitochondrial function, they showed in a retrospective before-after clinical study among consecutive septic patients that patients treated with intravenous vitamin C, hydrocortisone, and thiamine had markedly lower mortality rates (propensity-adjusted odds of mortality 0.13 (95% CI, 0.04–0.48) [91].

Only a few studies examined the effect of thiamine supplementation on mitochondrial function [92–94]. A recent study found significantly lower lactate levels in patients with thiamine deficiencies after supplementation with thiamine (200 mg). Moreover, a lower mortality rate was found in thiamine-deficient patients receiving thiamine supplementation compared with placebo. However, these effects were not found in the total study population [94]. In addition, in 20 burn patients an association between serum thiamine levels and lactate levels ($r = 0.016$; $p = 0.002$) was demonstrated [93]. On the contrary, thiamine supplementation (300 mg) before cardiac surgery did not significantly reduce lactate concentrations in a pilot study among 30 patients [92].

3.1.2. Riboflavin (vitamin B2)

Levels of riboflavin have barely been studied during critical illness. Shenkin and colleagues found an association between lower riboflavin levels and a higher mortality in 152 critically ill patients [95]. In a study with 80 critically ill children, where the elevation of glutathione reductase was used as an indicator for riboflavin deficiency, 3.8% was deficient [88]. By contrast, another study in 125 critically ill patients and 119 healthy controls showed significantly elevated plasma riboflavin and flavin mononucleotide concentrations and significantly reduced concentrations of FAD among critically ill patients. In addition, the ratio of plasma FAD to riboflavin was much lower in critically ill patients compared with controls. These results indicate disturbances in plasma FAD and riboflavin metabolism [96]. A small study in 4 patients with mitochondrial myopathy, associated with complex I deficiency, showed normalization of complex I activity after treatment with riboflavin [97].

3.1.3. Cobalamin (vitamin B12)

Vitamin B12 levels in a normal range (191–663 pg/mL) [98] are essential during critical illness. Remarkably, data on the associations between plasma vitamin B12 levels, disease severity, and outcome appear to be non-consistent. Both deficiencies, but also elevated levels have been found to be associated with adverse

Table 1
Studies assessing mitochondrial function in critically ill patients.

Author	Year	Study population	Design	Samples	Methods	Outcomes	Main results
Brealey et al., [19]	2002	28 ICU patients and 9 control patients (hip surgery)	Cross-sectional	Muscle biopsy within 24 h of ICU admission	Mitochondrial complex activities were measured by spectrophotometry, Adjusted for citrate synthase activity. ATP, ADP and AMP were measured by reverse-phase high-performance liquid chromatography.	Skeletal muscle mass ATP concentrations	Muscle ATP concentrations were significantly lower in the 12 septic patients who died compared with those (16) who survived (7.6 nmoL/mg dry weight vs 15.8; $p < 0.001$) and controls (7.6 vs 12.5; $p = 0.05$). Increased complex I activity was associated with less severe septic shock and increased concentrations of reduced glutathione and ATP.
Fredriksson et al., 2006 [21]		10 ICU with sepsis induced multi-organ failure and 10 metabolically healthy age- and sex-matched control patients (elective surgery)	Cross-sectional	Muscle biopsies from vastus lateralis (leg) and serratus anterior muscles.	Complex I and IV activity was assessed using spectrophotometric assays. ATP and creatine phosphate concentrations were measured enzymatically. The morphological evaluation was done by a trained pathologist using a Tecnai 10 electron microscope.	Activity citrate synthases and complexes I and IV. Concentrations ATP, creatine phosphate and lactate. Morphology mitochondria.	Lower activity of citrate synthases (53%) and complex I (60%) in rib muscle but not in leg muscle compared with controls. The activity of complex IV was 30% lower in leg muscle but not in rib muscle. Concentrations of ATP (40%) and creatine phosphate (34%) were lower and lactate concentrations 43% higher in leg muscle. Both in leg and in rib muscle a twofold decrease in mitochondrial content was found.
Fredriksson et al. [22],	2008	17 ICU patients and 10 age-matched controls	Cross-sectional	Skeletal muscle biopsies	Activities of citrate synthases, complex I and IV were assessed using spectrophotometry. Mitochondrial protein synthesis was assessed using gas chromatography-mass spectrometry analysis.	Transcript profiling (mitochondrial genes)	Muscle mitochondrial enzyme (citrate synthases, complex I and IV) activities are decreased with sepsis (−25%, −49% and −33% respectively). However, in isolated mitochondrial complex IV activity was increased in septic patients (+60%) compared to controls. Neither *in vivo* protein synthesis nor the expression of mitochondrial genes was compromised.
Fredriksson et al. [20],	2009	7 healthy male volunteers received endotoxin challenge	Trial	Skeletal muscle biopsies (before, 2 and 4 h after challenge).	Mitochondrial citrate synthases, complexes I and IV activity were measured using spectrophotometric assays on a Konelab analyser.	Maximal activities of citrate synthase and complex I and IV.	Activities of citrate synthase and complex I were significantly increased 2 h after endotoxin challenge (+16% and +68% respectively). No changes in ATP, creatine phosphate or lactate.
Jiroutkova et al. [15],	2015	8 ventilated patients with ICU-acquired weakness and 8 age and sex-matched metabolically healthy controls.	Cross-sectional	Muscle biopsies (of m. vastus lateralis).	Spectrophotometric analyses were used to assess the activities of the individual complexes.	Activities of respiratory complexes	The ability of aerobic ATP synthesis was reduced in 54% of ICU patients. This was correlated to depletion of complexes III (38% of controls; $p = 0.02$) and IV (26% of controls, $p < 0.01$) without signs of mitochondrial uncoupling. When adjusted for citrate synthase, the activity of complexes I and IV was not different, while the activity of complexes II (3 fold) and III (3 fold) were increased in ICU patients. Non-survivors of septic shock showed a significant lower complex I and higher complex IV activity expressed per citrate synthase activity compared with survivors and healthy controls

Notes: ATP: Adenosine triphosphate; ICU: intensive care unit.

effects. Critically ill patients have been found to be at risk of cobalamin deficiency, especially those patients suffering from burns and severe trauma, elderly, patients receiving chronic renal replacement therapy, patients who underwent gastric surgery or are suffering from bowel disorders [99]. Vitamin B12 deficiency is associated with megaloblastic anaemia and demyelinating neurological diseases [100]. At the same time, other studies have reported two-fold higher vitamin B12 levels in non-survivors compared with survivors [98,101]. Even after adjustment for APACHE score, age, chronic diseases, sepsis and ventilation, elevated vitamin B12 levels remained associated with higher mortality [101]. Yet another study found no association between high vitamin B12 levels and mortality risk after adjusting for liver functions [102]. To our knowledge, there are no published studies assessing the effect of vitamin B12 on mitochondrial function specifically in ICU patients.

Table 2
Potential relevant food component functions in energy metabolism and mitochondrial function.

Food components	Relevant functions	Problems in deficiency	Recommended Dietary Allowance (RDA) or adequate intake (AI) [39–41]	Remarks
Water-soluble vitamins				
Thiamin (vitamin B1) Active form thiamine pyrophosphate	Cofactor for cytosolic transketolase and PDH Cofactor for mitochondrial α-KGDH and branched-chain ketoacid dehydrogenase [42]	Impaired aerobic metabolism due to a reduced ability of pyruvate to enter TCA cycle resulting in lactic acidosis [43].	>19 year Men: 1.2 mg/day Women: 1.1 mg/day	
Riboflavin (vitamin B2)	Flavoprotein precursor and key building block for complexes I and II Involved in beta-oxidation (TCA cycle) The precursor of flavin adenine dinucleotide (FAD)and flavin mononucleotide (FMN) [42]	FAD-dependent dehydrogenase inhibition resulting in impaired mitochondrial oxidation of fatty acids and branched amino-acids [44].	>19 year Men: 1.1 mg/day Women: 0.9 mg/day	
Niacin (vitamin B3)	Precursor of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Involved in glycolysis and TCA cycle [42].	Decreased overall energy production	>19 year Men: 16 mg/day Women: 14 mg/day	
Pantothenic acid (vitamin B5)	Precursor of CoA and therefore crucial in the function of PDH and α-KGDH [42].	Impaired functioning of PDH and α-KGDH resulting in reduced ability to generate energy from fatty acids.	>19 year Men: 5 mg/day Women: 5 mg/day	
Biotin (vitamin B7)	Coenzyme of five mitochondrial carboxylases and essential for normal mitochondrial and cellular function. Essential for fatty acid oxidation and gluconeogenesis [42].	Impaired fatty acid oxidation and gluconeogenesis.	* >19 year Men: 30 μg/day Women: 30 μg/day	
Folate (vitamin B9)	Initiation of mitochondrial protein synthesis Synthesis of glycine Cleavage of serine to 5,10-methyltetrahydrofolate (needed for synthesis of purines and thymidylate) [45].	Decreased ATP formation and DNA synthesis [45].	>19 year Men: 320 μg/day of dietary folate equivalents Women: 400 μg/day of dietary folate equivalents	
Cobalamin (vitamin B12) 2-deoxyadenosyl (ado) form	Required for the synthesis of succinyl CoA from methylmalonyl-CoA Regulation of NF-κB, via inhibition of inducible NOS Antioxidant and anti-inflammatory properties Central role in hematopoiesis [45,46].	Decreases ATP production and possible complex I activity. Impaired bacteriostasis and phagocytosis [47]	>19 year Men: 2.4 μg/day Women: 2.4 μg/day	
Ascorbic acid (vitamin C)	Antioxidant [48], but could act as pro-oxidant in high concentrations [49]. Involved in the biosynthesis of carnitine, the key factor in beta-oxidation [50]. Cofactor for the synthesis of catecholamines, which in turn stimulate the oxidation of carbohydrates to generate energy [76]	Impaired beta-oxidation, impaired ATP production	>19 years Men: 90 mg/day Women: 75 mg/day	
Fat-soluble vitamins				
Tocopherol (vitamin E) Bioactive form α-tocopherol	Vitamin E is the most important lipid-soluble antioxidant in cell membranes [51–53]. Oxidized TQ cause a down-regulation of respiratory activity Essential cofactor in desaturation of saturated fatty acids [54].	TQ arising from excessive oxidative degradation of tocopherol can interfere with complex I, II and III activity [55].	>19 years Men: 15 mg/day Women: 15 mg/day	
Trace elements				
Selenium	Involved in mitochondrial biogenesis; stimulate PGC-1α and NRF-1 Antioxidant (glutathione peroxidase, glutathione reductase) [38,56]. Attenuate ischemia-activated autophagy [57,58].	Impaired mitochondrial biogenesis	>19 years Men: 55 μg/day Women: 55 μg/day	The Canadian Clinical Practise Guidelines at present have advised against high dose selenium supplementation, as the evidence is overall inconclusive [59]
Zinc	High levels can inhibit glycolysis and the TCA cycle [97] Antioxidant [60] Important in DNA synthesis, cell proliferation, protein synthesis and cell membrane integrity [38]	Inhibition of glycolysis by Zn occurs by negatively affecting important enzymes such as glyceraldehydes-3-phosphate dehydrogenase and phosphofructokinase [61]. High levels of zinc inhibit α-KGDH [62] and several other enzymes [63,64] leading to decreased ATP production [64].	>19 years Men: 11 mg/day Women: 8 mg/day	
Bioactive substances				
Coenzyme Q10			Not applicable	

(*continued on next page*)

Table 2 (*continued*)

Food components	Relevant functions	Problems in deficiency	Recommended Dietary Allowance (RDA) or adequate intake (AI) [39–41]	Remarks
	Electron acceptor complex I and II [65] Antioxidant [66]	Impaired activity complex I and II resulting in decreased ATP production		
Caffeine	Inhibit cyclic adenosine monophosphate (cAMP)-phosphodiesterase. This inhibition leads to increased levels of cAMP and the activation of protein kinase A [67]. Increases cAMP resulting in increased effectiveness of complexes I and IV [68].	Decreased ATP production due to impaired functioning of complexes I and IV.	Not applicable	
Melatonin	Sleep regulation Antioxidant [69] can inhibit the activity of mitochondrial nitric oxide synthase, which is assumed to play a pivotal role in sepsis [70] Stimulates complexes I and IV, probably by scavenging of ROS, especially peroxynitrite and nitric oxide [69,71,72].	Decreased ATP production due to impaired functioning of complexes I and IV.	Not applicable	
Carnitine	Transport of long-chain fatty acids through the mitochondrial membrane wherein these substrates undergo β oxidation Stimulates PDH and the TCA cycle Maintaining CoA pool	Carnitine depletion could result in impaired beta-oxidation, which results in acyl-CoA accumulation and depletion of CoA pool, in turn, resulting in mitochondrial dysfunction, reduced ATP production and increased oxidative stress [73].	Not applicable	
Creatine/creatine phosphate	Important temporal and spatial energy source.	Hypophosphatemia results in impaired cellular energy stores, due to depletion of cellular ATP, which in turn result in neuromuscular abnormalities and mitochondrial dysfunction [145].	Not applicable	Serum phosphate levels are carefully monitored in critically ill patients and repleted with intravenous and/or enteral phosphate.
Nitrate	Partial inhibition of mitochondrial respiration, due to binding to complex IV [33,34] Stimulates mitochondrial biogenesis depending on guanosine 3,5 monophosphate, mediated by the induction of PGC-1α [74]. May regulate tissue protein expression and activation, independently of NO formation [75].	Lower ATP production rate and decreased mitochondrial efficiency.	Not applicable	
Lipoic acid	Antioxidant [76]. Involved in energy production as it is an essential cofactor in mitochondrial dehydrogenase complexes [77] Improves mitochondrial function and insulin sensitivity by activation AMPK and PGC-1α [78,79].	Decreased ATP production.	Not applicable	
Taurine	Role in mitochondrial protein translation. Induce phosphorylation of PDH [75,79,80,143,145]. Suggested to act as a pH buffer in the mitochondrial matrix to stabilize beta-oxidation of fatty acids [81].	The decrease in mitochondrial respiration and activity of complex I and III [80].	Not applicable	Although these mechanisms would suggest potential beneficial effects of taurine supplementation, it is not taken up by muscles after oral administration, despite increased plasma concentrations [82].

3.1.4. Other B vitamins

The role of niacin, pantothenic acid, biotin and folate in mitochondrial function and energy metabolism has been described in detail previously [42,45]. To our knowledge, no studies have been performed in critically ill patients assessing the status of these B vitamins and their associations with clinical outcomes and/or mitochondrial function.

3.2. Ascorbic acid (vitamin C)

Levels of vitamin C are significantly lower in critically ill patients compared with healthy controls [103–105]. In addition, vitamin C deficiency is associated with increased risk of mortality. Several trials found a positive effect of vitamin C supplementation on clinical outcomes, including ICU and hospital length of stay [106,107], as well as mortality [108].

Castro and colleagues found inhibition of glucose transport and activation of lactate transport with high intracellular ascorbic acid in neurons expressing the GLUT1, GLUT3, sodium vitamin C transporters and monocarboxylate transporters [109]. The clinical consequences of these vitamin C-associated alterations in carbohydrate metabolism have not been determined yet. To our knowledge, no studies have been published assessing the effects of vitamin C on mitochondrial function in critically ill patients. Effects of vitamin C administration on muscle energy metabolism have been studied in athletes [110,111], who may take vitamin C supplements to limit oxidative stress related to intense exercise. Remarkably, vitamin C supplementation was found to decrease

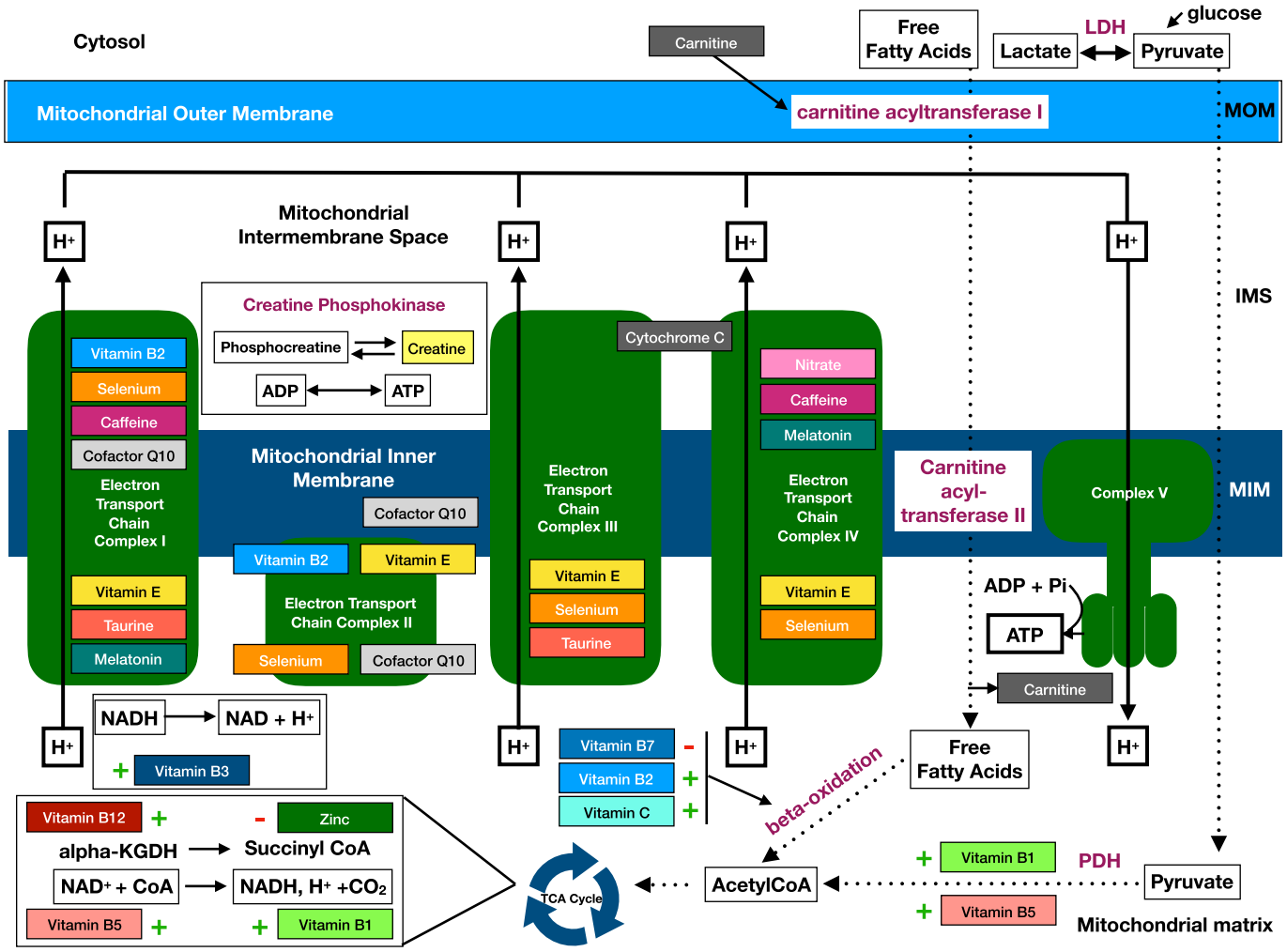

Fig. 3. Overview of relevant nutrients in bioenergetic mitochondrial processes. Several nutrients are involved in the formation of acetyl CoA, which is essential in energy production as it is the starting point of the TCA cycle. Thiamine (vitamin B1) is essential for the conversion of pyruvate to acetyl-coA. Furthermore, high levels of zinc were found to inhibit the glycolysis and TCA cycle. Carnitine is essential in βeta-oxidation of free fatty acids. In addition to the formation of acetyl CoA, several nutrients have an direct effect on the TCA cycle. Pantothenic acid (vitamin B5) is the precursor of CoA. Vitamin B 12 is an essential cofactor in the formation of succinyl-CoA, an important metabolite of the TCA cycle. Besides, several nutrients influences the activity of the electron transport chain. Niacin (vitamin B3) is the precursor of NAD^+, which has a crucial role in the formation of NADH, which on turn plays a crucial role in the electron transport chain. Complex I and IV activity is decreased during critical illness, but several nutrients positively affect complex I and IV performance. Complex I and IV may be stimulated by selenium, caffeine and melatonin. Complex I and II are also stimulated by CoQ10. Taurine depletion is associated with impaired activity of complexes I and III. Whether the effect of vitamin E on the complexes I and IV is stimulating or inhibiting has not yet been revealed. Nitrate probably inhibits complex IV activity. Riboflavin (vitamin B2) is an important building block for complexes I and II and involved in fatty acid oxidation in the TCA cycle. α-KGDH: alpha-ketoglutarate dehydrogenase; ATP: adenosine triphosphate; CoA: coenzyme A; CO_2: carbon dioxide; CoQ: coenzyme Q; NAD(H): Nicotinamide adenine dinucleotide (reduced); PDH: pyruvate dehydrogenase; Vit: vitamin.

cellular adaptations to exercise, by hampering mitochondrial biogenesis via a reduction of the expression of PGC1α, NRF1, and Tfam. In addition, vitamin C prevented the exercise-induced expression of cytochrome C (part of complex IV) [110,111]. Furthermore, the increase in the maximal rate of oxygen consumption was lower in athletes who received vitamin C supplements compared with the non-supplemented controls [110].

3.3. Tocopherol (vitamin E)

A study in rats showed that a mitochondrial targeted vitamin E compound (Mito-Vit-E) was able to increase complex IV activity in the liver of septic rats compared with control rats [112]. Furthermore, Mito-Vit-E protected mitochondrial structure and function in heart cells by maintaining mitochondrial membrane integrity, recovery of respiratory function and reduction of lipid and protein oxidation [113].

To our knowledge, no studies were performed on critically ill patients assessing the effect of vitamin E on mitochondrial function.

3.4. Selenium

Results from *in-vitro* studies in hippocampal neuronal cells have suggested that pre-treatment with Se limits the effect of hypoxia on mitochondrial complexes by normalizing complex I and IV levels and significantly improving complex II and III activity compared with non-Se treated cells. These effects may be associated with modulation of Akt and cAMP response element binding. Selenium availability changes during critical illness. During systemic inflammation, selenium and other vitamins and minerals are redistributed to tissues involved in protein synthesis and immune cell proliferation [114]. Several studies indicate that Se status is associated with clinical outcome [115–118]. These studies found

that Se levels were lower in critically ill patients compared with healthy controls and that Se levels decrease during critical illness. In addition, low Se concentrations were associated with worse clinical outcomes such as new organ failure and mortality [115,117,118]. Furthermore, non-survivors had lower levels of Se at ICU admission and subsequent ICU stay [116].

Many studies assessing the effect of Se on mortality in critically ill patients were done, with conflicting results [38]. To our knowledge, no studies assessing the effect of Se on the respiratory chain and mitochondrial function in critically ill patients have been done yet.

3.5. Zinc

Due to alterations in zinc disposition during the systemic inflammatory response, it is difficult to diagnose true zinc deficiency. Lower zinc plasma levels were associated with higher diseases severity. However, no differences in zinc levels were found between survivors and non-survivors [119–122].

To our knowledge, no studies assessing the effect of zinc supplementation on mitochondrial function in critically ill patients have been published.

3.6. Coenzyme Q10

Already decades ago it was shown that levels of CoQ10 were associated with the activity of complex I and complex II/III [123].

Several studies found lower levels of CoQ10 in critically ill patients compared with healthy controls [124–127]. Donnino and colleagues reported significantly lower CoQ10 levels in patients with septic shock compared with healthy controls (0.49 μmoL/L vs 0.95 μmoL/L) [127]. In addition, lower CoQ10 levels after cardiac arrest compared with healthy controls were found (0.28 μmoL/L vs 0.75 μmoL/L). Furthermore, lower CoQ10 levels were associated with poor neurologic outcome and increased mortality risk [126]. However, in both studies of Coppadoro and colleagues, no associations between CoQ10 and mortality were found [124,125].

In vitro, CoQ10 decreased oxidative stress and maintained mitochondrial membrane potential [128]. In addition, a recent randomized double-blind pilot trial showed that supplementation with ubiquinol (the reduced form of CoQ10) was able to improve CoQ10 levels in patients with septic shock [129]. However, an RCT in 30 patients with mitochondrial cytopathy receiving 1200 mg/day CoQ10 showed only minor effects of CoQ10 on ergometer cycling exercise aerobic capacity and post-exercise lactate, and no effect on strength or resting lactate [130]. Further studies are warranted to address whether administration of CoQ10 can result in improved clinical outcomes and mitochondrial function in critically ill patients.

3.7. Caffeine

Results of a study in 120 septic rats suggest that caffeine may stimulate oxidative phosphorylation, by restoring complex IV activity. This study also suggested a significantly better survival after caffeine administration [131].

3.8. Melatonin

A study in mice has demonstrated that melatonin rescued mitochondria from oxidative stress-induced mitochondrial dysfunction and may prevent subsequent cell death of muscle cells [132]. Several *in vitro* and *in vivo* studies demonstrate that melatonin affects mitochondria by increasing the activity of the electron transfer system and ATP production, increasing mitochondrial membrane potential and membrane fluidity and by closing the mitochondrial permeability pore [71,112,133–135].

Several small studies measured melatonin levels in critically ill patients. Circadian rhythm of melatonin secretion was disturbed and melatonin secretion low in almost all critically ill patients investigated [136–139]. Low levels of melatonin were associated with more severe illness in septic patients, but not in patients admitted for coronary syndrome, intoxications, gastrointestinal bleeding, pneumonia or stroke [136]. Melatonin supplementation was also found to reduce oxidative stress and inflammation in newborns with sepsis [140]. No published studies were found on the effect of melatonin supplementation on mitochondrial function and clinical outcomes in critically ill patients. However, the study of Mistraletti and co-workers showed a good bioavailability of exogenous melatonin in critically ill patients [141].

3.9. Carnitine

Carnitine depletion could be expected in patients who undergo prolonged continuous renal replacement therapy, parenteral nutrition for more than 14 days, hypertriglyceridemia or hyperlactatemia [73]. Primary carnitine deficiency, caused by defects in plasma membrane carnitine transporters in kidney and muscle is uncommon. However, secondary deficiency, caused by disease or as a side-effect of medication, can occur. Indeed, this is observed in conditions with increased catabolism as in critical illness [142,143]. Only a few studies assessed the effect of carnitine supplementation on clinical outcome [144,145]. Carnitine supplementation appeared to improve outcome in sepsis [144] and acute heart failure [145]. Notwithstanding its importance for beta-oxidation and subsequent mitochondrial energy production [73], effects of carnitine supplementation on mitochondrial function in critical illness have not been studied yet. In general, it is suggested that carnitine supplementation, although not indicated in the healthy population, may be of value in situations characterized by low concentrations of L-carnitine or impaired beta-oxidation, for example, to achieve a higher level of exercise performance [146–148].

3.10. Nitrate

A study in healthy volunteers showed a better coupling between respiration and oxidative phosphorylation after nitrate treatment (0.1 mmoL/kg/day, divided into three doses). Also, a higher maximal ATP production rate and improved mitochondrial efficiency were found. In addition, results of this study indicate a decreased proton leakage. Finally, mitochondrial density and biogenesis were not affected by nitrate treatment for three days [75]. Nitrate appears to enhance mitochondrial efficiency in healthy persons and probably in populations suffering from muscle weakness and exercise intolerance [149]. However, in critically ill, in particular, in septic patients, NO production is increased, due to (over) stimulation of the innate immune system [149]. An even further increase in nitrate/NO levels could be potentially harmful. A study in patients with mitochondrial myopathy did not find an effect of nitrate supplementation for a week on oxygen cost of moderate exercise and mitochondrial function [150]. Taken together, nitrate supplementation could be beneficial for survivors of critical illness, but should not be administered to patients during the acute phase of critical illness.

3.11. A-Lipoic acid

Evidence of an effect of lipoic acid on mitochondrial function in humans is limited. A case report describing a woman with chronic progressive external ophthalmoplegia and muscle mitochondrial

DNA deletion showed an increased exercise slope of the work-energy cost transfer function reflecting improved mitochondrial activity in muscle, after treatment with 600 mg LA daily for one month [151]. An RCT assessing the effect of a combination of LA, CoQ10, and creatine in patients with mitochondrial disorders found a reduction in oxidative stress, resting lactate levels and positive changes in body composition [152].

4. Discussion and perspectives

Our review of the available literature on changes in mitochondrial function during critical illness reveals several knowledge gaps and inconsistencies. The available data suggest that mitochondrial respiration is decreased in muscle cells. Literature also underlines that several nutritional components are pivotal to mitochondrial functioning and that optimizing their availability hold promise to improve the clinical outcome of critical illness. Together, these components form a complex network (Fig. 2). Importantly, mitochondrial bio-energetic functioning will be optimal when substrates and cofactors in this network are available in optimal combinations. Combined deficiencies are probably more common than those of single-nutrient and therefore investigation of combined deficiencies and the role of combined supplementation will be of great interest. Consequently, it is difficult to draw conclusions on the effects of a single nutrient in the oxidative phosphorylation process, as many nutrients cooperate in metabolic pathways. It is likely that supplementation with one nutrient does not improve downstream effects when there is a deficiency of another micronutrient. To make it even more complicated, for almost all described components we lack detailed information on the (normal) status or recommended daily allowance and their association with mitochondrial function and mortality. Furthermore, it is questionable whether plasma levels of nutrients reflect actual availability in mitochondria. Plasma nutrient levels may be low during critical illness due to increased losses through body fluids and increased permeability of endothelium, redistribution, altered protein binding, and inadequate intake. As a consequence, their plasma levels do not likely reflect tissue storages of micronutrients during critical illness. This makes it even harder to interpret the associations found: Is it really a causal inference or does it represent an epiphenomenon only indicating the severity of the disease or even is it reflecting an adaptive response? Moreover, for many nutrients, beneficial effects were only shown in small non-randomized, open-labelled studies and not in large RCTs [153]. Besides, some specific mitochondrial targeting nutrients are developed, such as MitoE and MitoQ, These nutrients are probably more effective in restoring bio-energetic functioning than just restoring plasma levels of the specific micronutrients [154,155].

It should also be kept in mind that bio-energetic failure of the mitochondria is not the only cause of ICU-acquired weakness. Other factors, including but not limited to altered muscle membrane excitability due to sodium and calcium channel abnormalities and excitation-contraction uncoupling due to altered calcium homeostasis and myofibrillar calcium insensitivity are important processes in muscle weakness [14].

4.1. Recommended research

Although this field holds several promises, much remains to be investigated on the underlying mechanisms and potential of targeted nutritional intervention in preventing or combating negative health outcomes of critical illness. Important gaps exist 1) in relation to our general knowledge on mitochondrial dysfunction during disease, both on the short- and the long-term, and 2) the effects of nutritional components, in particular in combination in human patients during different stages of the disease process. Regarding the first point, well-controlled cohort studies seem warranted in which monitoring of health parameters is combined with physiological and biochemical measurements. Ideally, these studies should include metabolic and functional parameters of muscle tissue. To measure mitochondrial function, *in vitro* or *ex vivo* strategies have been used, which provides information on maximal (OXPHOS) enzyme activities using saturated metabolites. Although this is very informative it does not take the nutritional status of the patients into account. Therefore, this field of research would greatly benefit from *in vivo* (non-invasive) real-time assessments of mitochondrial function. Approaches that could be used are 1) indirect calorimetry to measure *in vivo* substrate oxidation [156], 2) Phosphorus NMR spectroscopy to measure phosphocreatine, ATP, inorganic phosphate, and 3) near-infrared spectroscopy (NIRS) to measure *in vivo* muscle oxygen consumption [157]. This altogether provides a wealth of information on *in vivo* mitochondrial functioning. Next to this, transcriptomic and proteomic (muscle, immune cells) and metabolomic (urine) analyses will help to find biomarkers and to reveal underlying mechanisms. Regarding the second point, there is currently insufficient knowledge on the role of combinations of nutrients to stimulate mitochondrial function in critically ill patients. Even information on `normal' plasma and tissue levels of micronutrients during critical illness is often lacking. Despite the limitation that plasma levels do not necessarily reflect what happens in tissues, such information remains useful, in particular when performed as part of cohort studies following patients during and after their discharge from the ICU.

Nutritional intervention and (or) supplementation studies should address the issue of combined effects, supplementation with single nutrients is discouraged. When performing such studies, bio-availability and other kinetic factors, as well as the real-time assessment of mitochondrial function should be considered. Translational studies may be warranted to assess the effects of supplementation with one or more substance(s) on mitochondrial function.

5. Conclusion

Taken together, the evidence that impairment of mitochondrial bio-energetic function in muscle plays a crucial role in determining recovery from critical illness is convincing. As the underlying mechanisms involve different pathways and processes, 'multiple-target' strategies are best suited to correct the imbalances. Promising candidate molecules include several nutritional components.

Authors contribution

E. Wesselink and A.R.H. van Zanten contributed to the conception and design of the manuscript. E Wesselink contributed to the acquisition and interpretation of the data. E. Wesselink drafted the manuscript. W.A.C Koekkoek, S. Grefte, R.F. Witkamp and A.R.H van Zanten critically revised the manuscript. All authors approved the final version.

Conflicts of interest

Dr. van Zanten reported that he has received honoraria for advisory board meetings, lectures, and travel expenses from Abbott, Baxter, BBraun, Danone-Nutricia, Fresenius Kabi, Lyric, and Nestlé-Novartis. Inclusion fees for patients in the MetaPlus trial from Nutricia were paid to the local ICU research foundation.

The remaining authors have disclosed that they do not have any conflicts of interest.

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