REVIEW ARTICLE

NEW INSIGHTS ABOUT THE EFFECT OF IMMUNO-NUTRITION ON THE OUTCOME OF THE SERIOUSLY ILL PATIENT, A NARRATIVE REVIEW

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Abstract

Background: Acute illness is associated with hypercatabolic state, immunosuppression and inflammation. The role of immuno-nutrition (IN) in critically ill patients is still controversial although the use of immunomodulators has been shown to be beneficial. The purpose of this study was to explore the effect of immuno-nutrition on the outcome of the seriously ill patient. **Methods**: A 2000-2021 literature review was performed to analyze and evaluate the scientific base evidence for the use of immune nutrients (such as arginine, glutamine, omega-3 fatty acids and antioxidants) in critically ill patients including COVID-19 infected patients. The review includes randomized controlled trial studies, systematic reviews and meta-analyses. **Results**: IN has been shown to improve immune suppression, inflammatory responses, mucosal barrier function and cellular defense function. Supplementing micronutrients could also act as metabolic support. Benefits are mainly concerning the effect on mortality, reduction in infectious morbidity in hemodynamic stable patients, significant reduction in the duration of respiratory engineering support, infection-related mortality, and length of hospital stay. IN formulas can mainly be used in certain groups of critically ill patients (severely gastrointestinal patients) in patients with burns, head or neck cancer, and in patients with mechanical respiratory support) and with caution in patients with severe sepsis. Concerning the COVID-19 infected patients there are not enough data on efficacy and safety.**Conclusions**: The mechanism by which IN modulates immune function and tissue repair processes is somewhat selective and may depend on metabolic, genetic, or environmental influences. It is still necessary to determine which are the most effective mixtures of immune elements, which nutrients are unnecessary and which nutrients can even prove harmful.

Keywords: Immuno-nutrition, critical illness, arginine, glutamine, omega-3 fatty acids and antioxidants

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INTRODUCTION

Severely ill patients are those who are at high risk for life-threatening conditions. These patients need hospitalization in the intensive care unit for immediate treatment of their condition. It includes perioperative patients, the severely injured, patients with severe burns, with respiratory dysfunction requiring mechanical ventilation, with severe metabolic disorders, patients with multiple organ dysfunction[1] or severe infection such as COVID-19. The stress caused by the severe pathological condition of the patient, causes in the first phase shock that lasts from a few to 24 hours and is characterized by loss of fluid in the interstitial space, mainly due to dysfunction of the epithelium of the gastrointestinal tract and is accompanied by a drop in temperature and reduction of energy consumption. It is a protective mechanism during conditions accompanied by hemodynamic instability. It is rapidly followed (<24 hours), by the flow phase that is distinguished in the catabolic and anabolic phase. The catabolic phase lasts from a few days to weeks and is characterized by over-metabolism and over-catabolism, resulting in an increase in temperature and energy consumption.[2]

It is common for a state of immunosuppression and inflammation to follow. In critical illness, this response is characterized by a secretion of proimflammatory mediators such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), and a compensatory expression of anti-inflammatory proteins such as IL-10 and the IL-1 receptor antagonist proteins.[3] The proinflammatory cytokines induces a disturbance of the body's hormonal balance followed by fat mobilization (lipolysis), protein mobilization (proteolysis), increased gluconeogenesis in the liver and a negative nitrogen balance. Consequence is weight loss, loss of skeletal muscle and adipose tissue, increase in basal metabolism (depending on stress level) and consequent increase in oxygen consumption, oxidative stress and other genomic driven metabolic effects.[3]

Released secondary inflammatory mediators, reactive oxygen intermediates, prostaglandins and leukotrienes lead to vascular permeability, designed to increase oxygen and nutrient delivery to injured tissues. During critical illness the adaptive immune response causes a decrease in a number of circulating dendritic cells and an increase apoptosis of lymphocytes. Also, there was observed a reduction in T cell responsiveness with impaired antibody response to a T cell antigen.[4]

Great difficulties are incurred by the clinicians concerning the management of critically ill COVID-19 infected patients. Up to 30% of coronavirus patients are presenting with an acute respiratory distress syndrome (ARDS) requiring urgent respiratory and hemodynamic support in the intensive care unit (ICU). COVID-19 colonizes the respiratory, gastrointestinal and neurological systems and sometimes also kidneys creating cell damage which induces high inflammation response. The imbalance between pro-inflammatory and anti-inflammatory cytokines, leads to the CRS (cytokine release syndrome), an excessive and damaging host inflammation which could lead to polyorganic dysfunction.[5]

The aim of this review was to overview the evidence of the role of immuno-nutrition in critical illness today.

METHODOLOGY

This review was performed from literature searches of PubMed, Google Scholar and Scopus for publications from the last 21 years (2000–2021) that have the terms immuno-nutrition and critical illness in their titles. The review includes randomized controlled trial studies, systematic reviews and meta-analyses. Of the 90 papers reviewed, only 59 met the inclusion criteria to be summarized in this review. Studies from the previous two decades are cited as supportive material.

Nutritional support to a seriously ill patient

The purpose of therapeutic nutritional support is to reveal pre-existing malnutrition, prevent additional protein and calorie deficiencies, optimize the patient's current condition and reduce further morbidity.

The outcome of patients with poor food intake is characterized by high mortality and morbidity, including immunosuppression, inability to heal wounds, infections, and organ failure.[6] The dietary targets added to critically ill patients are: reducing the effects of starvation, avoiding hyper / malnutrition, and preventing vital dysfunctions such as cardiorespiratory function, immune function, and others leading to a prolonged ICU stay.[7]

Malnutrition common in the ICU (16-20%), reduces wound healing capacity, reduces defense function and increases the risk of sepsis, systemic inflammatory response syndrome (SIRS), and multi organ dysfunction syndrome (MODS), threatening life of each patient.[8] These patients are clinically hypermetabolic with a low survival rate. The nutritional status of the patient in the ICU is one of the factors that affect the duration of mechanical respiration, the length of stay in the ICU, the frequency of infections and consequently the final outcome.[9]

Immuno-nutrition

Immuno-nutrition (IN) refers to the administration of increased doses of micronutrients to support the immune system during periods of organic stress.[10]

IN mainly aims to improve the metabolic and immune dysfunction of severely ill patients. The effectiveness of this diet varies based on the pathophysiology and severity of patient differences.[11] IN has been shown to be beneficial modulating the inflammatory response to injury, infection and improving clinical outcome.

Immunostimulants with adjuvant action include vitamins, minerals, fatty acids or amino acids. Glutamine, arginine, omega-3 and omega-6 fatty acids, nucleotides and antioxidants such as Vitamins A, C, D have been mainly studied.[12]

Clear value of the individual immunostimulants is lacking, but there are 3 clearly defined targets for the above immune-metabolic modulating substrates: The mucosal barrier function, the cellular defense function and the local or systemic inflammation. The mentioned targets are necessary in order to treat, stabilize and resuscitate the hypercatabolic, hyperdynamic critically ill patient.[4]

Selected immuno-nutrients with base evidence effectiveness

Glutamine

In catabolic states, glutamine is released from muscle tissue for energy production, and for the synthesis of the antioxidant glutathione.[13] Glutamine increases T-lymphocyte response, β-lymphocyte differentiation, antibody production, phagocytosis and neutrophil function.[14]

Glutamine helps maintain the function of the barrier in the intestinal mucosa by inhibiting the expression of pro-inflammatory proteins.[15,16] Glutamine also protects against damage caused by pro-inflammatory agents by activating heat-shock cell proteins in response to oxidative damage, lethal heat (burns), and ischemia-reperfusion conditions.[17] In addition, the protective effect of glutamine is associated with its participation in the production of arginine.[18]

In clinical studies the administration of glutamine (mainly parenterally) it has been found to reduce the frequency of systemic infections thanks to the maintenance of the function of the intestinal barrier, controlling bacterial translocation.[19] Randomized studies in patients with severe trauma and burns have shown that enteral glutamine administration reduces the complications of infections and potentially lower mortality through the effects on the intestinal epithelium and maintenance of gut integrity.[20,21] It has also been found to reduce the incidence of multi-organ dysfunction syndrome and death associated with infection in severely ill patients. These results are contradictory with the Hey-

land et al.,[22] trial which showed higher rates of mortality at 6 months in the group with multisystem organ failure that received glutamine.

There are many randomized controlled studies and meta-analyzes investigating the effectiveness of glutamine in supplementary therapy in acute stressful diseases. In many of meta-analyzes, it was confirmed that glutamine had a positive effect on recovery time, development of secondary infection and mortality.[23]

In addition, a recent study on critically ill patients with COVID-19infection shows that adding enteral L-glutamine to the normal nutrition in the early period of infection can shorten the length of the hospital stay and reduce the need for ICU.[24] In contrast, other studies have shown that glutamine is not recommended in case of COVID-19 infected patients with respiratory failure. There is no recommendation for parenteral glutamine.[25]

Arginine

It is a semi essential amino acid that is taken up by both the diet and the endogenous synthesis through the entero-renal axis of citrulline. Arginine plays a central role in the urea cycle, and is a major mechanism of detoxification of ammonia. It is important for cell regeneration and for the formation of the immune response.[26] L-Arginine is the only substrate for the production of nitric acid (NO). Arginase and nitric acid synthase compete for arginine as a substrate, and the metabolic products of these enzymes are important regulators of T-lymphocyte function and production.[27] As a precursor to nitric acid, it contributes to vasodilation, reduction of platelet concentration, stimulation of macrophages, regulation of cardiovascular function and stability.[28] Regarding the use of arginine enterally in a diet enriched with arginine, omega-3 fatty acids and nucleotides has been found to improve healing, and hospitalization time in severe injuries. With these indications the specific preparation is recommended by ESPEN.[29] In contrast, in ICU patients in critical condition and patients with severe burns it has not been shown to be beneficial.[30] Studies using a formulation with at least 12 gm /1000 calories of arginine showed a significantly reduced mortality and better outcome of patients in the ICU. Lower levels may increase mortality in septic patients.[27] The best practice is to use with fish oil in surgical ICU patients. Currently it is not recommended for medical ICU patients, ARDS and sepsis patients.[4]

On the other hand, recent studies concerning severely ill patients infected with COVID-19 showed the importance of arginine depletion. Arginine is an important nutrient essential in the lifecycle of many DNA and RNA viruses, and therapeutic depletion of arginine may therefore inhibit SARS-CoV-2 replication. In addition, arginine plays an important role in the host inflammatory response, and reduction of serum plasma arginine levels could plausibly attenuate the severe inflammatory response.[31]

Nucleotides

They are important for cell division, tissue proliferation and immunoregulation. Their bioavailability is critical for frequently dividing cells such as white blood cells and intestinal cells. Nucleotides are essential components for the synthesis of coenzymes FAD, NAD and coenzyme CoA. They are obtained from the diet and synthesized de novo in the body. [32] Their parenteral administration (mainly α-purine and α-pyrimidine) in the diet, increases the activity of macrophages, maturation, blastogenesis and T-cell function. Administration of ribonucleotides reduces the production of proinflammatory cytokines such as IL-12. [33] Their beneficial effect is seen both in the modification of the intestinal microflora and in the maintenance of the integrity of the intestinal mucosal barrier, they contribute to the reduction of bacterial migration in cases of sepsis.[34]

Clinical trials in a pediatric population demonstrated that nucleotide supplementation in infant formula milk positively affects lipid metabolism, resistance to infection, growth and development. Nucleotide-enriched diets decreased the prevalence of infectious complications and length of hospital stay in patients with GI cancer undergoing major elective surgery, but in those studies

nucleotides were used in an admixture together with other immunonutrients making it difficult to discern the specific physiologic beneficial effects of the nucleotides.[35] Nucleotide administration is recommended also to surgical ICU patients.[4]

Non report concerning the nucleotide supplementation in critical ill patients infected with COVID-19 was found.

Omega-3 fatty acids

Omega-3 fatty acids (specifically EPA and DHA) have strong anti-inflammatory activity associated with reduced activity of arachidonic acid metabolites such as prostaglandins, leukotriene B4 and thromboxane A2. They reduce chemotaxis, leukocyte activation, and expression of pro-inflammatory agents.[36,37] They also enhance bacterial killing by macrophages and increase tissue regeneration.[38] Omega-3 has been found to act by transporting arachidonic acid from the cell membrane, reducing the action of NFKβ, the transcription factor AP1, possibly reducing nitric acid production and iNOS protein expression.[39] Omega-3 PUFA promotes antithrombotic effects, maintain tissue perfusion, improve graft function, increase tolerance to organ transplantation and decrease incidence of cardiac arrhythmias.[40]

Regarding the clinical use of omega-3 fatty acids, contradictory results have been found regarding their parenteral administration to ICU patients in relation to mortality. However, favorable results have been found in other clinical variables, such as hospitalization time, septic complications, antibiotic needs, oxygenation, staying out of mechanical respiratory function for a longer period and a shorter stay in the ICU, as well as immediate improvement of their hypofunctional systems.[41] Administration of omega-3 long-chain fatty acids reduces the risk of developing pressure ulcers in patients in the ICU. [42] Regarding the administration of fish oil: it was found that it reduces the time spent in the ICU but not the total time of hospitalization. It also reduces the time of respiratory mechanical support.[43]

In critical ill COVID-19 patients, taken into consideration their enhanced state of inflammation linked with ARDS, omega-3 polyunsaturated fatty acids could be a pivotal important component of immuno-nutrition: omega-3 fatty acids modulate neutrophil function, reduce the secretion of proinflammatory cytokines by macrophages, and reduce the reactive oxygen species. Omega-3 fatty acids decrease inflammatory responses through their effects on eicosanoid production and specific cytokines.[44]

Coagulopathy is commonly observed in critically ill COVID-19 infected patients as disseminated intravascular coagulation that could be present in the majority of deaths may be induced by sepsis.[45] In trials with healthy participants it was demonstrated that EPA and DHA induce a decrease in platelet aggregation and thromboxane release via COX-1 and 12-LOX activation.[46] A recent randomized, double-blind, clinical trial on 128 critically ill patients infected with COVID-19 has shown that omega-3 supplementation has beneficial effects on respiratory function, on acidosis and renal function maybe due the avoiding of microemboli in renal vessels which is a consequence of the prothrombotic state results in kidney damage as well as reducing the ischemia induced renal inflammation. [47]

Antioxidants

In severely ill patients, oxidative stress has been associated with cell damage, enhanced response to the systemic inflammatory response syndrome (SIRS), and increased mortality. [39] The best known antioxidants are superoxide dismutase, catalase, glutathione peroxidase, which work with the help of their catalysts such as selenium, iron, manganese, copper and zinc. Vitamins A, D and E, as well as phenols, polyphenols and flavonoids are potential free radical scavengers.[16] Research has shown that decreased selenium levels correlate negatively with the level of systemic inflammatory response in patients in the ICU.[48] Regarding the administration of vitamins C and E to patients in the ICU, a reduction in pulmonary mortality and the prevalence of multi-organ dysfunction was observed. [49] The administration of antioxidants to patients in the ICU reduces mortality,

protects against multiple organ failure, reduces the length of stay in the ICU, and the duration of mechanical ventilation.[50-51]

Antioxidants are associated with a significant reduction in mortality, infection complications, and respiratory support time. Concerning the COVID-19 severely ill infected patients there is no evidence from completed randomized controlled trials to conclusively and specifically demonstrate a role for vitamin supplementation in the fight against COVID-19, although there is strong scientific evidence, based on studies of vitamin physiology in clinical studies which indicates a beneficial role for vitamins.[52]

Vitamin A

The biological functions of vitamin A, involves gene transcription through the recruitment of coactivators that decondensate chromatin and enable transcription of target genes, epithelial and membrane regulation, bone metabolism, and antioxidative properties.[53] Mainly it has a crucial role in immune system modulation. Vitamin A has been found to not only promote proliferation of T-lymphocytes (through the increase of IL-2) but to also promote their differentiation, especially into regulatory T cells. This is also a key regulator of immune function for humoral defense of viral and gastrointestinal infections and for maintaining immune tolerance to harmless antigens especially in gastrointestinal tract.[54]

Administration of vitamin A has been used in critically ill patients as part of an antioxidant cocktail, but its role is still controversial in this group of patients. A randomized controlled trial evaluating the use of vitamin A (100,000 IU intramuscular) in thirty-two patients with severe sepsis showed no significant differences in ICU length of stay, time on mechanical ventilation, time on blood pressure agents, or 28-day mortality rates.[55,56]

Regarding critically ill patients infected by COVID-19, bioinformatics findings indicate vitamin A could have a beneficial pharmacological activity for the treatment via associated cytoprotection, anti-inflammatory, immunoregulatory and anti-viral effects Using the network pharmacology strategy to uncover the molecular functions, the beneficial effects of vitamin A for COVID-19 infected patients could be shown via the modulation of the gene expression of genes such as MAPK1, IL10, EGFR, ICAM1, MAPK14, CAT, and PRKCB. [57]

Vitamin C

Vitamin C, which is also known as ascorbic acid, plays a key role in iron and folic acid metabolism. This nutrient supports epithelial barrier function against pathogens, cellular functions of the adaptive and innate immune systems, and protects against oxidative stress during the respiratory burst as evidenced by the high concentrations of vitamin C found in polymorphonuclear granulocytes mainly in the monocytes and mononuclear lymphocytes. Vitamin C has also been shown to promote the proliferation, differentiation and maturation of T- and possibly also B-lymphocytes.[58]

In clinical trial vitamin C administered intravenously at high-doses (66 mg/kg/hr) in the first 24 hours following severe burn injury reduced volume requirements during fluid resuscitation and therefore lessened body weight gain and edema of the wound. Time on mechanical ventilation was also noted to be statistically significantly reduced. There was also observed an effect on reducing fluid resuscitation requirements in burn injuries as well as an improvement in urine output. There was no difference in hospital length of stay, time on mechanical ventilation, mortality or incidence of ventilator-associated pneumonia.[59]

Concerning critical ill COVID-19 infected patients only small clinical studies regarding prevention of COVID-19 with vitamin C supplementation were found. Although some clinical observations reported an improved medical condition of critically ill patients with COVID-19 treated with vitamin C concerning a shorter duration of hospitalization, improved their respiratory symptoms and oxygen saturation as well as decreased risk of mortality. [60]

Vitamin D

Last year's research focused on vitamin D and its functions regarding the regulation of the immune system. Most immune cells carry the vitamin D receptor on their surface allowing the conversion of 25-(OH)-vitamin D (25-(OH)-D) to its active form.[61]

Vitamin D is related to the suppression of pro-inflammatory cytokines and induces an overall tolerogenic immune response. Vitamin D plays a crucial role in the body's microbiota function and composition and therefore in epithelial barrier function.[62]

Vitamin D deficiency has been associated with deficiently pulmonary function during viral and bacterial infections, as well as in non-infectious diseases of the lung like asthma.

A clinical trial on critically ill children found sepsis related to low vitamin D levels, but there was no statistically significant difference in length of PICU, mortality, duration of mechanical ventilation.[63] The VITdAL-ICU trial realized in heterogeneous critically ill patients demonstrated in a secondary outcome, in patients with severe vitamin D deficiency, that high-dose oral vitamin D3 improved mortality.[64] Recent clinical study in critical ill COVID-19infected patients demonstrated that the majority of COVID-19 ARDS patients had vitamin D deficiency. 25-hydroxyvitamin D status was not correlated to changes in clinical course, although decrease levels of 1,25-dihydroxyvitamin D were associated with a worse APACHE II score and prolonged mechanical ventilation.[65]

CONCLUSIONS

In the great majority of studies, the prevailing opinion has been that critical ill patients could benefit from IN, mainly malnourished patients. High nutrition risk identifies those patients most likely to benefit from early IN therapy. The beneficial effects of enteral IN compared with parenteral IN are well documented in numerous RCTs involving a variety of patient populations in critical illness. Benefits are mainly concerning the effect on mortality, reduction in infectious morbidity in hemodynamic stable patients.

Multiple meta-analyzes show that IN is associated with a significant reduction in the duration of respiratory engineering support, infection-related mortality, and length of hospital stay. The effect of immunotherapy is clearer in patients in the ICU and its beneficial effect is more effective if administered before surgery, mainly in terms of reducing mortality associated with infections. The results for the safety of arginine use in patients with severe sepsis are contradictory. Specific considerations may be taken for obese patients. According to the international nutritional associations (eg ASPEN, ESPEN) guidelines, IN formulas (with agents such as arginine, glutamine, nucleic acids, omega-3 fatty acids, and antioxidants) can only be used in certain groups of critically ill patients (severely gastrointestinal patients) in patients with burns, head or neck cancer, and in patients with mechanical respiratory support) and with caution in patients with severe sepsis. Concerning the COVID-19 infected patients there are not enough data on efficacy and safety.

The results from clinical trials suggest that the mechanism by which IN modulates immune function and tissue repair processes is somewhat selective and may depend on metabolic, genetic, or environmental influences.

The need remains for well-controlled studies that will determine the ideal composition and dose of nutrients in the IN in order to achieve the best result for patients. It is necessary to determine which are the most effective mixtures of immune elements, which nutrients are unnecessary and which nutrients can even prove harmful.

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