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Glutamine as an Immunonutrient

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Dietary supplementation with nutrients enhancing immune function is beneficial in patients with surgical and critical illness. Malnutrition and immune dysfunction are common features in hospitalized patients. Specific nutrients with immunological and pharmacological effects, when consumed in amounts above the daily requirement, are referred to as immune-enhancing nutrients or immunonutrients. Supplementation of immunonutrients is important especially for patients with immunodeficiency, virus or overwhelming infections accompanied by a state of malnutrition. Representative immunonutrients are arginine, omega-3 fatty acids, glutamine, nucleotides, beta-carotene, and/or branched-chain amino acids. Glutamine is the most abundant amino acid and performs multiple roles in human body. However, glutamine is depleted from muscle stores during severe metabolic stress including sepsis and major surgery. Therefore it is considered conditionally essential under these conditions. This review discusses the physiological role of glutamine, mode and dose for glutamine administration, as well as improvement of certain disease state after glutamine supplementation. Even though immunonutrition has not been widely assimilated by clinicians other than nutritionists, immunonutrients including glutamine may exert beneficial influence on diverse patient populations.

Key Words: Glutamine, immune dysfunction, malnutrition, critical illness

INTRODUCTION

A number of clinical studies have investigated the beneficial effects of enteral[1,2] or parenteral[3,4] nutrition after surgery, trauma, infection, starvation, or injury. Even though the mechanisms by which nutrients improve certain disease states have not yet been clarified, reduction of morbidity and shorter length of stay in septic patients,[5] as well as reduced wound infection in burn patients[6] were demonstrated after enteral feeding of nutrients. Critically ill patients who received the immune formula had more rapid restoration of lymphocyte mitogenesis, reduction in infectious complications, and reduced mortality than those who did not.[7] Therefore, clinicians and nutritionists have focused on the composition of the nutrient mix. Arginine and omega-3 fatty acids with or without glutamine, nucleotides, beta-carotene, and/or branched-chain amino acids are important nutrients in the formula.[8] They are referred to as immune-enhancing nutrients. The term "immunonutrition" has been

based on the concept that malnutrition impairs immune function.[9] In immunonutrition, supranormal quantities of nutrients are supplied to achieve pharmacological effects via the enteral or parenteral route.[10]

In this review, one single nutrient, glutamine, is to be discussed, as it was previously omitted from most enteral feeding and all parenteral infusions. This may have been due to the fact that glutamine is abundant in the body and is thus not an essential amino acid. In addition, the solubility of glutamine is low in an aqueous environment, which makes glutamine inappropriate for enteral and parenteral nutrition. During catabolic stress (trauma, sepsis, burn), glutamine is rapidly released from muscle stores and serum, and intracellular levels of glutamine decrease.[11-13] Therefore, glutamine becomes conditionally essential under these conditions.[14] This review discusses whether the glutamine supplementing enhances the physiologic and immunologic functions of critically ill patients by summarizing the role of glutamine in the human body, types and doses of glutamine supplementation, and changes in disease states after glutamine administration.

PHYSIOLOGICAL ROLE

Glutamine provides fuel for rapidly dividing cells (particularly lymphocytes and enterocytes)[11] as well as the epithelial cells of the intestines.[15] Glutamine maintains gut barrier function, and is a precursor for the endogenous antioxidant glutathione.[10] It plays an important role in nitrogen transport within the body, and serves as a substrate for renal ammoniagenesis.[16] Glutamine induces the expression of heat shock proteins and stimulates nucleotide synthesis.[17] Signaling mediators such as extracellular signal-regulated protein kinases that regulate cell differentiation are activated by glutamine.[18] Glutamine contributes to mucin formation and intestinal surface integrity by mediating the synthesis of N-acetylglucosamine and N-acetylgalactosamine.[19]

Precursor for glutathione

Concentrations of glutathione are suboptimal in clinical conditions including HIV infection, hepatitis C infection, cirrhosis, type II diabetes, ulcerative colitis, and myocardial infarction. Three amino acids are needed to synthesize glutathione: glycine, glutamic acid and cysteine. Glutamine is easily converted to glutamic acid and produces an antioxidant glutathione.[20] Therefore, supplementation of glutamine may have beneficial effects for reducing symptoms of inflammatory disorders and may protect against the damaging effect of oxidative stress. Although glutamine is an important substrate for glutathione, its capacity to synthesize glutathione is influenced by the presence of cysteine and glycine. The supply of sulfur-containing amino acids that can be converted to cysteine is also important point to be considered for glutamine supplementation.

Intestinal mucosal integrity and immune function

Glutamine has an important role in cell-mediated immunity[21] and the integrity of the intestinal mucosa.[22] During severe metabolic stress (i.e., trauma, sepsis, major surgery, bone marrow transplant, chemotherapy and radiotherapy), glutamine stores are depleted.[1-3,23-29] Glutamine supplementation during illness increases gut barrier and lymphocyte function and preserves lean body mass. Glutamine protects against septic shock by preventing the depletion of glutathione and thus reducing cell death, which occurs during shock.[30] In surgical or cancer patients, glutamine supplementation decreases the production of some pro-inflammatory cytokines[31,32] which may be associated with inhibition of nuclear factor-κB and p38 mitogen-activated protein kinase in the intestinal mucosa by glutamine supplementation to Crohn's patients.[33]

Expression of heat shock protein

Heat shock protein plays a role in tissue protection after stress or injury, as its absence leads to an increase in cellular apoptosis. Glutamine induces expression of heat shock protein and reduces expression of inflammatory cytokines.[34] The effect of glutamine on the induction of heat shock protein may be related to the beneficial effects of glutamine supplementation, such as a decrease in length of hospital stay and ventilator time in critically ill patients.[35]

Conversion to arginine and reduction in insulin resistance

Glutamine is an important precursor for arginine through interorgan transport of citrulline.[36,37] In addition, glutamine reduces insulin resistance.[38]

Down-regulation of Toll-like receptor 4 (TLR4)

When the cells are exposed to lipopolysacharide, expression of TLR4 and signal adaptor protein MyD88 are upregulated, which leads to the induction of inflammatory cytokines such as TNF-α, IL-1 and IL-6 and intestinal mucosal

injury.[39] Enteral feeding of glutamine reduces the induction of TLR4, MyD88 and TRAF6 mRNA, and suppresses injury to the mucous membrane of the small intestines caused by LPS endotoxemia in rats.[40] Glutamine induced down-regulation of TLR4 expression in intestinal epithelial cells infected with gram-negative bacteria.[41] TLR4-dependent immune response and anti-bacterial/anti-inflammatory response after glutamine supplementation were reported in septic patients.[5]

MODE AND DOSE OF SUPPLEMENTATION

Glutamine dipeptide as a supplement

To overcome the low stability of glutamine in an aqueous environment, glutamine coupled with other amino acid (glycine or alanine) has been developed as a component of nutrient mix. Glutamine couples with alanine or glycine to form a less degradable dipeptide.[42] Both L-Glutamine and L-alanyl-L-glutamine prevented oxidant- or endotoxin-induced death of neonatal enterocytes *in vitro*.[43]

In humans, arterial glutamine concentrations were better after parenteral administration of alanyl-glutamine than after administration of free glutamine.[44] Peritonitis patients who received a solution containing L-alanyl-L-glutamine had lower mortality rates than those who received nutrition that did not.[45]

Dry-packing of glutamine and proteins rich in glutamine

Glutamine is easily degraded in a solution into a toxic product-pyroglutamate-particularly during heat sterilization. Therefore, formulas with free glutamine amino acids are packaged dry and reconstituted just prior to administration. Proteins rich in glutamine could be used as a glutamine supplement to avoid toxicity issues in prepared liquid formulas.[8] A recent study showed that an arginine-supplemented immune enhancing diet increased plasma glutamine, possibly by enhancing de novo synthesis of glutamine from arginine in post-operative patients.[46] Interaction/inter-conversion of amino acids and nutrients is an important research field to be resolved in immunonutrition.

Doses of glutamine

Oral glutamine (0.3 g/kg body weight/day) administration showed beneficial effects on intestinal integrity and the overall incidence of necrotizing enterocolitis/septicemia in preterm infants.[47] Administration of enteral nutrition with a glutamine enriched formula (30.5 g/100 g protein feeding) resulted in a significant decrease in the incidence of pneumonia, bacteremia, and sepsis of critically ill patients as compared to control feeding (3.5 g/100 g protein).[48] Intravenous infusion of glutamine dipeptide as L-alanyl-glutamine (0.285 g/kg body weight/day) reduced the rate of mortality in critically ill patients.[49] Glutamine (0.4 g/kg body weight/day)-supplemented total parenteral nutrition significantly decreases leukocyte and natural killer cell count and therefore suppresses inflammation in patients with systemic inflammatory response syndrome.[50]

DISEASE STATE AFTER SUPPLEMENTATION

Severity of illness in patients in the intensive care unit (ICU) and septic patients

Patients in the ICU have low plasma glutamine concentrations (<0.42 mmol/L) at the time of admission, which may be related to the severity of their illness and high mortality rate.[51] Glutamine supplementation reduced infection and inflammation in critically ill patients, but the length of stay was not changed by glutamine supplementation.[10] In surgical or critically ill patients, the addition of glutamine reduced infection rates and shortened the length of hospital stay, but had no effect on mortality.[52] Although it is controversial as to whether glutamine supplementation reduces mortality or length of hospitalization in patients in the ICU and critically ill patients, supplementation does decrease their rate of infection and inflammation.

Patients undergoing chemotherapy and patients following hematopietic stem cell transplantation

Enteral feeding of glutamine reduced mucositis in chemotherapy patients[28] and in head and neck cancer patients with radiotheraphy.[29] Total parenteral nutrition with glutamine reduced the severity and duration of mucositis, and the duration of hospitalization for bone marrow transplant patients.[26,53] Glutamine dipeptide-supplemented total parenteral nutrition had no effect on neutropenic period, fever, extra antibiotics, or toxicity scores, but body weight gain per treatment cycle in catabolic hematologic patients with intensive chemotherapy.[27] Even though glutamine showed positive effects on mucositis of the gastrointestinal tract caused by

chemotherapy, radiotherapy and cancer cachexia with depletion of skeletal muscle glutamine,[28] the use of glutamine in this patient population is still up for debate. This is because glutamine can be an energy source for enterocytes and lymphocytes as well as malignant cells.

Short bowel syndrome and Crohn's disease

There was no evidence of beneficial effects of glutamine on gut function in short bowel syndrome patients.[54] Gut permeability was slightly improved by glutamine supplementation in patients with Crohn's disease.[33] In Crohn's disease patients, mucosal glutathione content is reduced as compared with controls. However, oral supplementation of glutamine had no effect on inflammation in humans.[55] A new formula has been suggested to increase glutamine efficacy at the site of mucosal lesions. Candidate amino acids such as arginine, glycine, and cysteine should be evaluated in the future.

Premature infants

Parenteral glutamine administration has dramatic results in premature infants. Glutamine-supplemented infants with a body weight lower than 800 g, required fewer days on total parenteral nutrition, had a shorter length of time to feed full, and needed less time on the ventilator.[56] Parenteral glutamine supplementation improved hepatic tolerance in infants with very low birth weights[57] and prevented sepsis.[58] Further large scale trials are needed to determine the efficacy of glutamine in these high-risk premature infants.

CONCLUSION

In general, glutamine supplementation reduces the rate of infection, inflammation, length of hospital stay, and mortality, and improves gut barrier function and immune function, especially cell-mediated immunity in critically ill patients. Future studies should focus on the type of formula, dose, delivery route, duration and timing of glutamine supplementation. Studies on disease-specific action mechanism of glutamine will be helpful for preventing secondary infection and disease progression. The combination of immunonutrients may have synergistic effects of the physiological and immunological function of individual nutrients. Inter-conversion and interaction of nutrients are the issues to be addressed. Inappropriate use of immunonutrients may be potentially harmful. Therefore, more detailed analysis of previous reports, including the pathogenesis of diseases, are required prior to supplementation of immunonutrients including glutamine. Immunonutrition may be potentially useful as a therapeutic modality with close communication and information exchange between clinicians and nutrition specialists.

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