Arginine and Immunonutrition: A Reevaluation

Arginine has been classified as a semiessential amino acid because of its nutritional requirement for the optimal growth of some species, but not humans. Over the past two decades, studies have shown arginine to be a powerful mediator of multiple biological processes including the release of several hormones, collagen synthesis during wound healing, antitumor activity, and immune cell responses. Although all hold significant interest to clinicians, the latter has the furthest reaching implications.

Early animal experiments have delineated some of the effects that arginine has on the immune system. Normal rodents given a 1% arginine HCl supplementation to their normal diet (1.8% arginine content) have demonstrated increased thymic weight secondary to increased numbers of total thymic T lymphocytes. This thymotropic effect correlates functionally with increased thymic lymphocyte blastogenesis in response to mitogens. Supplemental dietary arginine also minimizes or abrogates posttraumatic thymic involution and T cell suppression. In the athymic mouse, supplemental arginine increases the number of T cells and heights delayed-type hypersensitivity responses, suggesting a thymic-independent mechanism for the effect of arginine on T cell activity. Although the function of other cells of the immune system has not been studied after dietary arginine supplementation, there is increasing evidence that arginine and its metabolites are integral to the activity and interactions of macrophages and polymorphonuclear cells.

The clinical significance of arginine’s immunomodulatory ability has been evaluated primarily in experimental models of bacterial peritonitis and burns. Rats subjected to cecal ligation and puncture have demonstrated a significantly increased survival when given doses of 100 mg of arginine HCl by gavage three times a day; the survival advantage was further improved when gavage treatment preceded the onset of sepsis. Balb/C mice undergoing cecal ligation and puncture and fed a 2% arginine supplemented diet had a doubling of survival rates (28% to 56%). Guinea pigs subjected to 30% total body surface burns and supplemented with 2% arginine had a 30% greater survival rate. The same level of supplementation decreased bacterial translocation to liver and spleen in mice subjected to 20% body surface burn injury.

Human studies have shown that arginine increases T cell mitogenic responses when given at doses of 30 g/d. This effect has been noted in healthy volunteers and in severely ill intensive care patients. There is a lack of well-conducted studies examining the effect of arginine supplementation on clinical outcome benefits in patients.

Recently, special enteral diets have been formulated to contain high amounts of arginine together with ω-3 fatty acids, glutamine, and nucleic acids. The intent is to enhance or preserve the responsiveness of the cellular components of the immune system and/or to reduce harmful and exaggerated inflammatory responses. This therapeutic approach has been termed immunonutrition. Previous animal and human investigation has demonstrated that a supplementation of 5 to 12 g of arginine/1000 kcal induces enhanced T cell activity. The arginine concentrations of the commercially available dietary formulations vary greater than two-fold, but all contain higher amounts than those required for normal or postinjury nutrition (Fig. 1).

The concept of immunonutrition has gained much clinical
attention, and studies have been performed in an attempt to demonstrate clinical outcome benefits. Most published studies provide evidence of a potential clinical benefit from immunonutrition, yet they have small patient populations, which reduces statistical power. Recently, a meta-analysis of 12 randomized prospective studies using immunonutrition, encompassing a total of 1557 intensive care or postsurgical patients, has been accomplished. The major outcome measures analyzed include mortality, infection rates, days of mechanical ventilation, intensive care unit (ICU), and hospital length of stay. Immunonutrition had a strong and statistically significant effect in lowering the relative risk of developing infections to 0.6 (P = 0.005). Eight of the nine studies that measured infection rates (a total of 862 patients) demonstrated a decrease secondary to immunonutrition. Similarly, 9 of 11 studies (1273 patients) noted a significant (P = 0.0002) decrease in hospital length of stay, with an overall average decrease of 2.9 d for patients receiving immunonutrition. The five studies that reported ventilatory days (726 patients) demonstrated a decrease in ventilatory days for immunonutrition-treated patients by an average of 2.6 d (P = 0.04). Most surprisingly, the decrease in the risk of infection, the number of ventilator days, and length of stay in the ICU did not translate into survival advantage, overall mortality being equal between groups.

Many of the signs and symptoms of patients diagnosed with systemic inflammatory response syndrome, multiple organ dysfunction, or general septic states are a reflection of the body’s own inflammatory response to insult. Immunonutrition may aid patients with pathologic inflammatory responses by altering the composition of mediators of inflammation, such as prostaglandins, and by increasing immune responses, thus reducing the risk of infection.

Is the use of immunonutrition warranted for treatment of established infections or should it be used as an adjunct for reducing the risk of developing sepsis? Infection remains a serious problem both as a primary cause of illness and a secondary complication to surgical intervention or trauma. Sepsis continues to be a leading cause of morbidity and mortality. Although immunonutrition is associated with fewer infectious events, no benefit of immunonutrition supplementation was noted when given before elective major upper gastrointestinal surgery.

Despite ample evidence that arginine has the ability to activate cells of the immune system, its mechanism of action remains only partly defined. Intravenous infusion of a mixture of arginine and lysine increases autonomic nervous signals to the thymus while simultaneously decreasing sympathetic conduction to the spleen. Vagal stimulation of the thymus results in T cell release from this gland, whereas decreased splenic efferent activity potentially facilitates splenic natural killer (NK) cell activity.

On a cellular level, arginine is metabolized by a number of enzymes to various end products that are implicated in immunomodulation. Two of the more thoroughly investigated enzymes are arginase and nitric oxide (NO) synthase; each enzyme has multiple isoforms within mammalian organisms, and each isoform has tissue specificity.

Arginases act on arginine to produce urea and ornithine, and NO synthases liberate the highly reactive NO radical from arginine with concomitant formation of citrulline. Upregulation of both enzymes has been noted in response to various inflammatory/traumatic stimuli, ranging from mild, such as an incisional wound, to severe, as in systemic endotoxemia. Ornithine demonstrates most of arginine’s pharmacologic properties, including the seckatagogue, immune, and vulnerary activity, but cannot substitute nutritionally for arginine in organisms that require arginine for optimal growth. Although citrulline can nutritionally replace arginine, exogenous citrulline has none of the pharmacologic properties of arginine.

NO has multiple and not fully defined immune effects. It can act in an autocrine fashion within the various immune cells or in a paracrine fashion between immune cell populations. Arginine at low doses is essential for optimal human lymphocyte mitogenic responses in vitro; this requirement appears to be related to NO release. Conversely, macrophages stimulated to maximally produce NO greatly reduce the blastogenesis of cocultured lymphocytes. NO has also been implicated in the regulation of immune cells, in particular the commitment of T cells toward a TH2 phenotype. Perhaps the coexpression of arginase and NO synthase in macrophages represents a regulatory mechanism to modulate NO synthesis and arginine use during sepsis or heightened inflammatory responses.

The concept of immunonutrition is quite attractive, but until we understand more about the mechanism of action of the individual agents that are used for immunomodulation, we will not be able to optimize the ratio and concentration of the various elements used in immunonutrition. Individual agents should be used for immunonutrition in light of different pathophysiologic conditions and degrees of stress. As such, the relative doses of the individual substances, when administered in a combined formulation, may be key to achieving a positive immune response. Our bias is that arginine plays a major role in host immune function and that its effects in posttraumatic states should be studied. Whether arginine supplementation alone or as part of immunonutrition will be of benefit to immunocompromised patients remains to be fully investigated.

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REFERENCES