Immunonutrition

R. Singh,[1] S. Gopalan[2] and A. Sibal[1]

[1]Apollo Centre for Advanced Pediatrics, Indraprastha Apollo Hospital, [2]Pushpawati Singhania Research Institute for Liver Renal and Digestive Diseases (PSRI), New Delhi, India

Abstract. Nutrition and immunology are interrelated. Several nutrients like arginine, glutamine, omega-3-fatty acids and nucleotides enhance cellular immunity, modulate tumor cell metabolism and improve clinical outcome in stress situations. Glutamine supplementation has been shown to decrease incidence of sepsis and to reduce length of hospital stay in bone marrow transplant patients, low birth weight infants, surgical and multiple trauma patients. Studies with arginine have shown a reduction in infectious complications and lower mortality, however a better understanding of the biology of arginine is needed. Omega-3-fatty acid supplimentation as in fish oil stimulates the immune system. The beneficial effects of immunonutrition in surgical patients has been demonstrated inseveral studies. It significantly reduces infectious complications and length of hospital stay. In critically ill patients immunonutrition may decrease infectious complications but it is not associated with a mortality advantage. Pediatric experience is limited, but the future is promising. **[Indian J Pediatr 2002; 69 (5) : 417-419]**

Key words : *Immunonutrients; Glutamine; Arginine; Omega-3-fatty acid*

The term "immunonutrition" has been coined to describe diets that are specifically designed to enhance immune function. In recent years, nutrition and immunology are becoming interrelated disciplines and several nutrients have been shown to influence immunologic and inflammatory responses in humans. Whether these effects translate into an improvement in clinical outcomes in patients remain unclear. This paper briefly reviews the current knowledge in this area.

Trauma, surgery and critical illness induce hormonal, metabolic and inflammatory changes, that are commonly referred to as the stress response.[1] The resulting metabolic stress is characterized by glycolysis, lipolysis and proteolysis, which may escalate to an hypercatabolic response or "autocannabilism". These changes lead to a sequence of proinflammatory cascades leading to insufficiency of both specific and nonspecific immunocompetent cells and immunosuppression.[2]

Currently interest is focussed on the role of specific dietary components that could influence and alter the immune status of the body.[3] Most commonly used immunonutrient mixture contain omega 3 - fatty acids and the "conditionally essential" amino acids arginine, glutamine, cysteine and taurine. These compounds enhance cellular immunity, modulate tumour cell metabolism and cytokine production, augment lymphocyte and macrophage proliferation, improve wound healing and decrease nitrogen loss postoperatively.[5]

For many years, the best route for nutritional support was not clear and it is only in the past decade that there has been general aggrement that enteral feeding is the method of choice.[5] Intestinal ischemia and a corresponding impaired gut barrier function is thought to have a high impact on the development of multiple organ failure after severe trauma or critical illness. Under normal conditions the intestinal wall is a sufficient barrier against bacteria and their products. Gut ischemia is followed by mucosal lesions and the intestinal permeability is increased. Translocating bacteria and bacterial products (endotoxin, peptidoglycan) can lead to a local and/or systemic immuninflammatory response, which is held responsible for the development of multiple organ failure.[6] Early enteral nutrition decreases development of multiple organ failure.[6]

Glutamine

Glutamine serves as a fuel for gut enterocytes and is essential for cells involved in mediation of the immune response (lymphocytes, macrophages and neutrophils). It has been shown to decrease negative nitrogen balance, maintain muscle mass and gut integrity after major surgery[7] and in very low birth weight babies.[8] Glutamine enriched total parenteral nutrition (TPN) has been shown to improve net nitrogen balance, reduce third space fluid accumulation and shorten the length of hospital stay in bone marrow transplant patients.[9,10] During stress situations plasma and muscle glutamine stores are rapidly depleted because this is preferentially shunted as a fuel source towards visceral organs thus contributing to the immunosuppression observed in critically ill patients.[11]

A randomized, double blind study conducted by Griffiths and colleagues,[12] comparing glutamine supplemented total parenteral nutrition enteral nutrition

Reprint requests : Dr. Anupam Sibal, Senior Consultant Pediatric Gastroenterologist and Hepatologist, Apollo Centre for Advanced Pediatrics, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi. E-mail : asibal@ndf.vsnl.net.in

with isonitrogenous isocaloric controls in critically ill intensive care patients, showed better survival and reduced hospital costs in the former. In another well controlled study in trauma patients. Significant reductions in length of hospital stay, intraabdominal abscesses, infection rates and duration of antibiotic use were observed.[13]

Arginine

Arginine has a great potential as an immunomodulator and may prove useful in catabolic conditions such as severe sepsis and postoperative stress.[14,15] There is a body of evidence suggesting that supplemented arginine upregulates immune function and enhances wound healing.[14,15] Arginine stimulates the secretion of several hormones including the anabolic hormone insulin and prolactin and growth hormone. It may also be involved in local regulation of tissue blood flow as it is a precursor of nitric oxide.[16] Heylind *et al*[17] analyzed 22 randomized trials and found that studies using commercial formulas with high arginine content were associated with a significant reduction in infectious complications and a trend towards a lower mortality rate compared with other immune enhancing diets. Though the results from these studies in critically ill patients are far from definitive, they are promising that this mode of therapy may be of some advantage. A better understanding of the in vivo biology of arginine and its metabolism is necessary to truly define a benefit from arginine supplementation.[18,19]

Taurine

Taurine has intestinal protective effects along with glutamine and arginine during periods of stress. It has a key role in membrane stabilization, antioxidation, calcium homeostasis, apoptosis and osmoregulations.[20] The precise role remains to be defined.

Lipids and Immune Function

In several studies, medium chain triglycerides containing TPN has been demonstrated to decrease the production of tumour necrosis factor by stimulating monocytes compared to long chain triglycerides.[21] The polyunsaturated fatty acids are precursors of prostaglandins, leukotrienes and thromboxanes. An increase in the omega – 3 fatty acid composition of the diet relative to its omega-6 content (as in fish oil) would be predicted to yield more of the 3 series prostaglandins than the 2 series (since these are derived from omega – 6 fatty acids). As PGE 3 is a less potent inhibitor of the immune system than PGE2, omega 3-supplementation would be expected to stimulate the immune system.[22,23] Most commercially prepared parenteral and enteral nutrition formulas contain omega-6 fatty acids as the primary source of lipid. For this reason omega-3 fatty acids are being included as nutritional supplements for immunocompromised patients.[22,23]

Nucleotides

Dietary nucleotides are essential for cell mediated immunity and T lymphocyte function. In humans, nucleotide administration in the form of polyadenylic, polyuridylic acid as a therapeutic adjuvant has been shown to enhance natural killer cell cytotoxicity as well as disease free duration in the cancer patients undergoing surgery.[24,25]

Is Immunonutrition Beneficial?

The beneficial effects of early postoperative enteral immunonutrition on the immune system of patients after surgery have been demonstrated in several studies. Senkel *et al*[26] compared the efficacy of preoperative administration of oral immunonutrition with an isoenergetic control diet. In the immunonutrition group infectious complications and length of stay were significantly reduced. Thus despite higher product cost, immunonutrition appears cost effective due to substantial saving of resources used to treat postoperative complications.[27]

The effect of immunonutrition in critically ill patients may be systematically different from the treatment effect in elective surgical patients and recent clinical trials have shown conflicting and controversial results.[28] Atkinson *et al*[29] compared an immune enhancing formula with a standard formula in 398 critically ill patients. Patients who achieved early enteral immunonutrition had a significant reduction in their requirement for mechanical ventilation and associated reduction in length of hospital stay. However, patients receiving immunonutrition also tended to have an increased mortality rate and to die earlier. The study conducted by Bower *et al*[30] demonstrated that immunonutrition group had shorter length of hospital stay, but significant high mortality. In septic patients mortality was three times higher in immunonutrition group. It may be that excess mortality associated with immunonutrition is only observed in patients with sepsis.

The above results contrast with the recently completed multicenter study by Galbin and colleagues,[31] which demonstrated significantly lower ICU mortality in the immunonutrition group. But these benefits were observed in least sick patients (APACHE II<15), whereas there was no effect on mortality in sicker patients. Heyland *et al*[17,32] reviewed a total of 326 titles, abstracts and articles and concluded that immunonutrition may decrease infectious complication rates, but it is not associated with an overall mortality advantage in the critically ill.

CONCLUSION

The interrelationship between nutrition and laboratory parameters of immunity may have considerable practical applications. It is now clear that dietary composition can

profoundly affect immune function, cell division and interactions, the response to pharmacological agents and other biological processes. The number of large randomized placebo controlled trials is fairly limited, (with no experience in pediatric patients and observed effects are relatively small). Further research needs to define the underlying mechanism by which immunonutrition may be helpful and to identify which products and which patients are associated with clinical benefits. Metabolic modulation of immunity by specific nutrients may now hold promise of improving clinical outcome.

REFERENCES

1. Rolih CA, Ober KP. The endocrine response to critical illness. *Med Clin North Am* 1995; 79 : 211-214.
2. Meakins JL. Host defense mechanisms in surgical patients : effect of surgery and trauma. *Acta Chir Scand* 1988; 50 (suppl 5) : S 43- S 53.
3. Grimble RF. Nutritional modulation of immune function. *Proc Nutr Soc* 2001; 60(3) : 389-397.
4. "O" Leary MJ. Coakley JH. Nutrition and Immunonutrition. *Br J Anaesth* 1996; 77 : 118-127.
5. Heyland DK, Cook DJ, Duyatt GH. Enteral nutrition : a critical appraisal of the evidence. *Intensive Care Med* 1993; 19 : 435-442.
6. Grotz M, Regel G, Bastian L, Weimann A, Neuhoff K, Stalp K, Stalp M, Tercherne H. The intestine as the control organ in the development of multiple organ failure after severe trauma: pathophysiology and therapeutic approaches. *Zentralbl Chir* 1998; 123(3) : 205-217.
7. Hammerquist F, Wernerman J, Vander DA, Vinnars E. Alanylglutamine counteracts the depletion of free glutamine and the postoperative decline in protein synthesis in skeletal muscle. *Ann Surg* 1990; 213 : 637-642.
8. Neu J, Roig JC, Meetz WH. Enteral glutamine supplementation for very low birth weight infants decreases morbidity. *J Pediatr* 1993; 13 : 691.
9. Schloerb PR, Amare M. Total Parenteral nutrition with glutamine in bone marrow transplantation and other clinical applications. *J Parent Ent Nutr* 1993; 17 : 407-413.
10. Ziegler TR, Young LS, Benfell K, Scheltinga M, Hortos K, Bye R *et al.* Clinical and metabolic efficacy of glutamine supplemented parenteral nutrition after bone marrow transplantation. *Ann Intern Med* 1992; 116 : 821-828.
11. Parry BM, Baigrie RJ, Lamont PM, Morr's PJ, Newsholme EA. Effefts of major and minor surgery on plasma glutamine and cytokine levels. *Ann Surg* 1992; 127 : 1239-1240.
12. Griffiths RD, Jones C, Palmer TEA. Six month outcome of critically ill patients given glutamine supplemented parenteral nutrition. *Nutrition 1997; 13 : 295-302.*
13. Kudsk KA, Minard G, Croce MA, Brown RO, Lowrey TS, Pritchard FE *et al.* A randomized trial of isonitrogenous enteral diets after severe trauma : an immune enhancing diet reduces septic complications. *Ann Surg* 1996; 224 : 531-543.
14. Kennedy BC, Hall GM. Metabolic support of critically ill patients: Parenteral nutrition to immunonutrition. *Br J Anaes* 2000; 85(2) : 185-190.
15. Chang DW, De Santi L, Demling RH. Anticatabolic and anabolic strategies in critical illness : a review of current treatment modalities. *Shock* 1998; 10 : 150-160.
16. Gianotti L, Alexander JW, Pyles T, Fukushima R. Arginine – supplemented diets improve survival in gut derived sepsis and peritonitis by modulating bacterial clearance. The role of nitric oxide. *Ann Surg* 1993; 217 : 644-653.
17. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically all patients? A systematic review of the evidence. *JAMA* 2001; 286; 944-953.
18. Efran D, Barbul A. Role of arginine in immunonutrition. *J Gastroenterol* 2000; 35 (suppl) S20-S23.
19. Evoy D, Lieberman MD, Fahey TJ, Daly JM. Immunonutrition : the role of arginine. *Nutrition* 1998; 14 : 611-617.
20. Redmond HP, Stableton PP, Neary P, Bouchier HD. Immunonutrition: the role of taurine. *Nutrition* 1998; 14 : 599-604
21. Gogas CA, Zoumbos N, Makri M, Kalfarentzos F. Medium and long chain triglycerides have different effects on the synthesis of tumor necrosis factor by human mononuclear cells in patients under total parenteral nutrition. *J Am Coll* Nutr 1994; 13 : 40-44.
22. Grimm H, Kraus A. Immunonutrition : supplimentary aminoacids and fatty acids ameliorate immune deficiency in critically ill patients. *Arch Surg* 2001; 386(5) : 369-376.
23. Chuntrasakul C, Siltharm S, Sarasombath S, Sittapairochana C, Leo wattana W, Bunnak A *et al.* Metabolic and immune effects of dietary arginine, glutamine and omega – 3 fatty acids supplementation in immuno compromised patients. *J Med Assoc Thai* 1998; 81(5) : 334-343.
24. Lacour J, Laplancha A, Malafosse M, Gallot D, Julien M, Rotman N *et al.* Poly adenylic polyuridylic acid as an adjuvant in resectable colorectal carcinoma: a six year follow-up analysis of a multicentric double blind randomised trial. *Eur J Surg Oncol* 1992; 18 : 599-604.
25. Khan AL, Richardson S, Drew J, Larsen F, Campbell M, Heys SD *et al.* Poly adenylic polyuridylic acid ehnances the natural cell mediated cytotoxicity in patients with breast cancer undergoing mastectomy. *Surgery* 1995; 118 : 531-538.
26. Senkel M, Zumtobel V, Bauer KH, Marpe B, Wolfram G, Frei A *et al.* Outcome and cost effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal surgery: a prospective randomized study. *Arch Surg* 1999; 134(12) : 1309-1316.
27. Gianotli L, Braga H, Frei A, Greiner RD, Carlo V. Health care resources consumed to treat postoperative infections: cost saving by perioperative immunonutrition. *Shock* 2000; 14(3) : 325-330.
28. Heyland DK, Drover J. Immune enhancing diets (letter). *Crit Care Med* 2000; 28 : 906.
29. Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double blind, controlled clinical trial of enteral immunonutrition in the critically ill. Guy's Hospital Intensive Care Group. *Crit Care Med* 1998; 26(7) : 1164-1172.
30. Bower RH, Cerra FB, Bershadsky B, Licari JJ, Hoyt DB, Jensen GL *et al.* Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides and fish oil in intensive care unit patients, results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med* 1995; 23 : 436-449.
31. Galban C, Montejo JC, Mesejo A, Marco P, Celaya S, Sanchez-Segura JM *et al.* An immune-enhancing enteral diet reduces the mortality rate and episodes of bacteremia in septic intensive care until patients. *Crit Care Med* 2000; 28 : 643-648.
32. Heyland DK, Novak F. Immunonutritionin critically ill patient : More harm than good? *JPEN* 2001; 25(2 suppl) S51-S57.