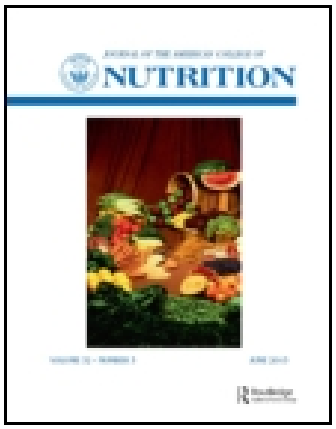

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Role of nutrition in the management of malnutrition and immune dysfunction of trauma.

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Role of Nutrition in the Management of Malnutrition and Immune Dysfunction of Trauma

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Current nutrition support improves patient outcome in trauma patients. It appears to do so by limiting the adverse effects of specific nutrient or generalized nutrient deficiencies. Immunosuppression, however, continues as a significant clinical problem. This immunosuppression appears to be part of the inflammatory response that accompanies trauma, and in part, to represent the need for conditional nutrients in this setting. Three nutrients that are being evaluated include arginine, uracil as ribonucleic acid and ω-3 polyunsaturated fatty acids. Animal studies report improved immune function. Early clinical trials are reporting improved immune function and patient outcomes.

Abbreviations: Arg = arginine, LPS = lipopolysaccharide, PgE2 = prostaglandin E_2, PMN = polymorphonuclear leukocytes, PUFA = polyunsaturated fatty acids, RNA = ribonucleic acid

INTRODUCTION

Initial attempt to nourish patients sustaining blunt or penetrating trauma were application of classic nutrition principles when patients appeared to manifest a rapidly developing form of malnutrition with associated organ dysfunction, nosocomial infections and wound failure. Nutrition support was provided as a potential therapeutic modality following control of hemorrhage, surgical therapy, and the restoration of oxygen transport. Some reduction in morbidity and mortality was observed, primarily related to the prevention of single nutrient or generalized nutrient deficiencies. The altered body composition and organ dysfunction of the disease process continued to persist.

The concept evolved that this phase of postresuscitative hypermetabolism represented a pathologic state of persistent inflammation with suppression of immune function. Eventually this pathologic process resulted in tissue parenchyme dysfunction and multiple organ failure. Research emphasis now is placed on learning when and how to modulate the processes of inflammation and repair, and immune function. The cells of greatest interest are the polymorphonuclear leukocytes (PMN), the macrophage and the lymphocyte, with research focus on modulation/regulation of those cells' function. Because of the potential roles of specific nutrients in these regulatory processes, several have been evaluated as potential tools for modulating inflammatory and immune function. This discussion will summarize the current status of nutrition support in trauma, and the rationale for using three nutrients; arginine (Arg), ω-3 polyunsaturated fatty acids (PUFA), and ribonucleic acid (RNA), to modulate inflammatory cell function.

THE CLINICAL SETTING

The normal response to a single event such as shock, soft tissue injury, or a major inflammatory focus such as pancreatitis, usually peaks on day 3 and spontaneously abates by day 7–10 postinjury [1–6]. In a subgroup of patients, particularly those experiencing more than one event such as hypovolemic hypotension followed by infection or unresolving pancreatitis, the response process does not abate and the phase of persistent hypermetabolism occurs, followed by organ failure in a large percentage of the patients [1–3].

Following resuscitation, the transition from normal recovery is usually heralded by acute lung injury requiring

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mechanical ventilation. A stable phase of several days then begins with either the lung injury as the dominant feature, or lung, liver and renal dysfunction concomitantly present. In a large percentage of patients, progressive deterioration of liver and renal function occurs and death ensues [4].

Identifiable risk factors for the transition to persistent hypermetabolism and organ failure include: shock; infection with sepsis; persistent inflammation as in pancreatitis; the presence of dead injured tissue, particularly muscle; the combination of a septic episode in the presence of a perfusion deficit; and recurrent episodes of one or more of the above. The physiology is characterized as hyperdynamic and the metabolism as hypermetabolic [3,5]. General characteristics are summarized in Table 1.

Current management consists of rapid and effective control of the inciting event, prevention of known risk factors, resuscitation of the microcirculation, and early institution of nutritional support. Source control and effective resuscitation have been associated with substantial reductions in morbidity and mortality [6,7]. Beneficial effects of nutritional support have been difficult to document. In part this has been related to developing techniques that minimize complications of nutrition support, determining the nutrition requirements of this group of patients over the 4–6 weeks of illness, and realizing that the disease process itself was a major contributor to the alterations in body composition. Analyses of prospective, randomized studies support the following in the presence of an adequate technique of administration [3,8,9]:

1. Nutrition support is associated with reduced morbidity and mortality.
2. The beneficial effects of nutrition support are related to prevention and/or treatment of single nutrient or generalized nutrient deficiency (Table 2).
3. Achieving caloric equilibrium does not appear to be advantageous.
4. Achieving or approaching nitrogen equilibrium does correlate with improved patient outcome.
5. Excessive doses of long-chain ω-6 PUFA may have adverse effects.
6. Immune dysfunction persists.

Achieving these results seems to be accomplished with a minimum of complications with the regimen presented in Table 3.

PATHOGENESIS OF THE RESPONSE TO INJURY RESULTING IN PERSISTENT HYPERMETABOLISM AND ORGAN FAILURE

In spite of current treatment, mortality and morbidity of patients responding to shock, resuscitation, and soft tissue injury with persistent hypermetabolism and organ

Table 1. Characteristics of Persistent Hypermetabolism

Clinical observations
1. Persistent inflammatory signs with alterations in temperature, PMN count, tachycardia, hyperventilation and encephalopathy
2. Nosocomial infections
3. Wound infections
4. Malnutrition with single and generalized nutrient deficiencies
5. Jaundice and oliguric renal failure
6. Immune dysfunction with energy, decreased antibody production and T cell proliferation in response to antigens and altered antigen presentation function

Physiologic observations
1. Increased oxygen consumption demand
2. Increased cardiac output and oxygen delivery
3. Increased demand for ventilation
4. Decreased systemic vascular resistance
5. Oxygen extraction failure in peripheral and visceral tissue beds

Metabolic observations
1. Increased gluconeogenesis and lipolysis that is relatively nonresponsive to exogenous glucose administration
2. Energy production by the process of aerobic glycolysis
3. Oxidation of a mixed carbon source for energy production: glucose, fatty acids of all chain length, and amino acids
4. Net total body catabolism that is poorly responsive to nutrition support
5. A rapid reduction in lean body mass that is poorly responsive to exogenous amino acids and anabolic hormones
6. Total body and hepatic protein synthesis that is responsive to exogenous amino acids until terminal organ failure ensues
7. A redistribution of the body nitrogen to areas of active protein synthesis such as the viscera, wounds, and white cell mass

Table 2. Single Nutrient Deficiencies

Amino acid	
BcAA LYS METH	More bacterial infections
ARG	T cell and macrophage function decreased
METH	Decreased complement levels (C3)
PHE/TYR	Decreased phagocyte function
Vitamins	
C	Reduced chemotaxia and random micration
A	Lymphoid atrophy; Decreased T and B function; Decreased phagocytosis
E	Antioxidant; High doses suppressant; Low doses stimulant to immune function
Trace elements	
Iron	Decreased phagocytic; Bactericidal activity
Zinc	Lymphoid atrophy; T and B cell dysfunction; Impaired phagocytosis
Selenium	Impaired antibody production; Cardiomyopathy

BcAA = branched chain amino acids, LYS = lysine, METH = methionine, ARG = arginine, PHE = phenylalanine, TYR = tyrosine.

Table 3. Guidelines to Maximize Benefits and to Minimize Complications by Adjusting Nutrient Loads to Metabolic Demands

1. Avoid calorie and glucose overload:
   a. Total kcal of 25–30 g/kg/day
   b. Glucose not to exceed 5 g/kg/day
   c. Maintain R/Q ≤ 0.9
2. Avoid fat overload:
   a. No more than 1.0 g/kg/day of current ω-6 PUFA formulations as a continuous infusion
3. Adequate doses of amino acids or protein
   a. 1.5–2.0 g/kg/day
   b. Modified formulations are more efficient with less ureagenesis, more nitrogen retention, and more effective support of protein synthesis
   c. Achieve nitrogen equilibrium; tolerate blood urea nitrogen < 110 mg/dl
   d. Response of visceral proteins depends on both adequacy of nutritional support and the magnitude of the inflammatory response and disregulation of organ failure
4. Multivitamins
   a. Balanced formula
   b. IV formulations require added vitamin K
5. Trace elements daily
   a. Magnesium 15–20 meq/day
   b. Zinc 15–20 mg/day

Glomerular filtration > 20 ml/min assumed for #5.

failure exceeds 50% [1,3]. The current nutrition approach, while supporting specific and generalized nutrient deficiencies, has little or no effect on the disease-related dysfunctions of the specific or nonspecific immune system. Thus, the response process itself may become the disease that is recognized as organ failure.

Details of the pathogenesis of the disease remain unclear. There is general recognition that the observed clinical responses reflect the interplay of cardiovascular physiology, cell metabolism and the neurohormonal mediator systems as they effect organ-specific and systemic functions. Some of these mediators are presented in Table 4.

During the shock and resuscitation portion of the clinical response spectrum, the location of the pathogenesis resides in the microcirculation and is mediated by platelets, endothelial cells, and PMNs [10]. The physiology is dominated by oxygen transport and its appropriate restoration. With the onset of postresuscitative hypermetabolism, the manifestations of organ injury become evident clinically, and the pathogenesis resides in the neurohormone-cytokine mediator systems, with the macrophage assuming an increasingly dominant role. Pathogenesis of the transition to progressive organ failure of membrane function as in signal transduction and second messenger generation [11], and on inappropriate or misdirected genetic modulation of cell and organ responses [12].

The observed clinical responses are not statistically different when analyzed by etiology, i.e., infection, pancreatitis, hypovolemic shock, and large soft tissue injury all present with similar signs and symptoms. Even with infections, different microorganisms may have different local manifestations, but the systemic responses are indistinguishable. These phenomena support the position that after control of the cause and appropriate circulatory resuscitation has occurred, a phase of systemic inflammation (persistent hypermetabolism) occurs and lasts for variable lengths of time and has variable outcomes. In those cases where the cause can be rapidly removed and resuscitation and supportive care rapidly begun, the hypermetabolism is short-lived and resuscitation delayed, inadequate or not possible, and multiple events occur such as nosocomial infection or hemorrhage, the critical course is prolonged. In other cases, the inflammation proceeds to repair what persists as fibroplasia. An example of the latter would be the fibrosing phase of adult respiratory distress syndrome. Finally, in another group, progressive organ failure occurs and death ensues [1–5].

Single agent attempts to attenuate or ameliorate the response, as with growth hormone or corticosteroids [13], inhibitors of eicosanoid production [14], and free radical scavengers, have not had substantial effect. With the realization that immune-dysfunction persisted even with nutrition support [15,16], research turned to the route and timing of nutrient administration. When nutrition was

Table 4. Mediators of the Response to Injury

Cytokines
Interleukin 1–8
Interferon γ
Platelet activating factor
Tumor necrosis factor
Eicosanoids
Prostaglandins (PGE_1, PGE_2, PGI_2)
Thromboxanes (TxA_2)
Leukotrienes (LTC_4, LTD_4)
Mediator amines
Histamine
Serotonin
Catecholamine
Octopamine
Opioids/other neurotransmitters
Hormone peptides
Thyroxine
Growth hormone
Insulin/glucagon
Cortisol
Cortical-releasing factors
Complement/kinin/coagulation
Matrix components
Growth factors
Enzymes
Proteases (acid and neutral)
Other lysosomal enzymes
Nitric oxide (derived from L-arginine)
Oxygen-derived intermediates

initiated 3–4 days after injury, the incidence and mortality of multiple organ failure syndrome is not altered by route of administration [17]. Enteral nutrition within 12–24 hours of injury, however, has been associated with less metabolic response to injury and fewer infections in animal models of burn injury and in small, prospective clinical trials in trauma patients [18–22]. Further clinical trials are now underway.

The translocation hypothesis implicates the gut aerobic flora in the pathogenesis of nosocomial infections and in the persistence of the hypermetabolic states. Experimental models indicate decreased effectiveness in the nucosal barrier function as the putative origin of the translocation phenomena [24]. A number of approaches are being evaluated to preserve the gut nucosal barrier and to reduce the effects of the translocating gut aerobic flora. These approaches range from nucosaltrophic agents such as enteral nutrition and supplementation of enteral diets with ketone bodies, branched chain amino acids or glutamine [25], to antibiotic regimens that are designed to selectively suppress the gut aerobic flora [26]. In the former case, data indicate that incidence of nosocomial infections can be significantly reduced. This reduction in nosocomial however, has not been accompanied by either a reduction in organ failure or mortality [26,27]. In addition, another study in trauma patients did not reveal the presence of bacteria or endotoxin when sequential sampling of the portal vein blood was performed after injury and resuscitation.

Other therapeutic approaches are modulating the processes of inflammation to promote wound healing, decrease organ dysfunction and failure, and return immune function to a homeostatic, responsive state. These approaches range from antibodies against PMN attachment receptors, interleukin receptors, endotoxin and tumor necrosis factor to finding clinically useful ways to directly effect second messenger generation and gene regulation. Speciality nutrients are in this latter category.

A number of nutrients are involved in second messenger generation, eicosanoid production and release, gene regulation, and lymphocyte proliferation in response to antigenic stimuli. The nutrients under evaluation are those targeted to modulate these functions by dose or composition. Nutrient deficiencies that could affect immune function, such as zinc deficiency, are successfully treated with current nutrition regimens. The speciality nutrients discussed here are ω-3 PUFA, Arg, and RNA.

ω-3 POLYUNSATURATED FATTY ACIDS

PUFA are major components of the cell membrane, and are responsible for the structural and functional integrity of those membranes, eicosanoid production and release, and signal transduction through the phospholipid-dependent second messenger pathways [28]. The major PUFA constituent of human cell membranes are the ω-6 PUFA family. There are very low levels of the ω-3 PUFA family, primarily resulting from the low intake of fish or plant oils high in these fatty acids in the North American diet. ω-3 PUFA can preferentially replace ω-6 PUFA [29], altering the physiologic characteristics of the membrane to such stimuli as lipopolysaccharide (LPS) or platelet-activating factor [30–32].

The incorporation of ω-3 PUFA such as 20:5ω-3 and 22:5ω-3 into macrophages and liver cells occurs within 3–6 hours in cell culture, and is stabilized and reflected in the plasma PUFA profile within a few days in vivo [28, 31]. Once incorporated, fluidity increases and inositol-phosphate production, dienoic eicosanoid release and interleukin and tumor necrosis factor release in response to LPS are reduced in vitro and in vivo [32–34].

The release of dienoic eicosanoids and tumor necrosis factor and interleukin-1 by the macrophage is related to both the ω-6/ω-3 ratio and ω-3 and ω-6 total PUFA content in the cell membrane in response to LPS stimulation. The trienoic eicosanoid release is increased. (These eicosanoids have similar functions to the dienoic prostaglandins, but have less potency.) A relative excess of linoleic acid substrate stimulates prostaglandin E_2 (PgE_2) production, which can decrease the ability of cytokines to stimulate interleukin-2 synthesis by endothelial cells, and suppresses T cell proliferative responses to lectin and specific antigen stimulation [28,32].

In animal models, ω-3 PUFA incorporation into hepatic macrophages and hepatocytes is stabilized in 3–5 days and is associated with reduced but adequate ω-6 PUFA content [31]. In rat models of bacterial peritonitis, ω-3 PUFA in the diet was associated with a reduction in mortality [33]. In the mouse popliteal lymph node assay system, dietary ω-3 PUFA restored lymphocyte proliferative responses to a magnitude equivalent to uracil administration [34].

Arginine

Arg is a semi-essential amino acid required for growth and cell division in posttraumatic states. It is a potent endocrine secretogogue that promotes the release of growth hormone, prolactin, insulin, and glucagon. In cell culture systems, Arg is essential for growth, but not for viability of cells or cytokine production and release. The putative origin of these effects resides in the biochemistry of Arg as an essential component on polyamine and nucleic acid synthesis [35–37].

Arg is also a major source of nitrous and nitric oxide in vitro and in vivo. These oxides are important mediators of vascular dilitation, and can inhibit protein synthesis and electron transport in hepatocytes [38]. Under experimental

conditions, a number of in vivo immune effects have been observed [39,40] including increased survival in septic animals; increased survival of tumor-bearing animals, a phenomenon associated with reduced tumor size; increased number of T cells and delayed type hypersensitivity responses in thymic nude mice; increased thymic and peripheral blood lymphocyte responses in in vitro assays of mitogen-induced blastogenesis; and increased allograft rejection in rodents. In humans, Arg has been associated with increased thymic and peripheral blood lymphocyte in in vitro blastogenic responses to mitogens, and preservation of these same responses in surgical patients. Recent data also suggest Arg supplementation is associated with a reduced length of stay following major cancer surgery.

Ribonucleic Acid

Purines and pyrimidines are precursors of deoxyribonucleic acid and RNA, which are necessary for protein synthesis and cell mitosis. Purines and pyrimidines have not been considered essential dietary nutrients. The liver has been suggested as a major source of endogenous purines and pyrimidines for other tissues. De novo synthesis from amino acids, bases or nucleosites from cell degregation can be reutilized through salvage pathways.

Restriction of dietary nucleotides results in suppression of cellular immune responses and prolongation of rodent allograft survival, presumably due to an inability of these T cells to undergo blastogenesis in response to antigenic stimuli [44]. Uracil administration can restore delayed hypersensitivity responses and T cell proliferative responses to specific antigens in mice [34] and can reduce abscess formation to gram-positive organism in the same system [45,46]. Dietary nucleotides may also be effective in macrophage activation of the T helper/inducer populations. Uracil has been reported to reverse the immunosuppression associated with blood transfusion in experimental settings. Such observations would support the position of an additional dietary requirement for purines and pyrimidines, or at least uracil, under conditions of metabolic stress.

COMBINATION THERAPY

Arg, RNA and ω-3 PUFA have been combined into a nutritionally complete enteral diet. The rationale was that the persistent inflammation observed in the clinical setting, in part, represented the presence of activated macrophages, and was associated with a suppression of T cell proliferative responses to specific antigens, possibly related to excess PgE_2 production and cytokine release from the activated marophages. It was hypothesized that ω-3 PUFA would decrease macrophage PgE_2 and cytokine release and stimulate T cell proliferative responses, and that Arg and RNA would directly stimulate T cell proliferative responses.

The first studies from these human trials indicate that the targeted nutrients are associated with a restoration of in vitro T cell proliferative responses to and above that of normal, nonstressed man [47,48]. This result seems to occur independently of the nutritional outcomes of visceral protein synthesis and the achievement of nitrogen balance. The control group demonstrated continued suppression of the in vitro immune function assays. Clinical outcome studies evaluating length of stay and the incidence of nosocomial infections are currently underway.

CONCLUSION

Thus, specific nutrients appear to be able to substantially alter cell-cell communication, metabolic regulation, and the ability of cells to respond to exogenous stimuli. It also appears as if these effects are not dependent on achieving traditional outcomes of nutrition support in critical patients; however, quality nutrition support is necessary to prevent the development of single nutrient or generalized nutrient deficiencies from becoming significant comorbidites or comortalities in patients with postresuscitative hypermetabolism and organ failure. Early clinical studies indicate a restoration of immune function and beneficial clinical outcomes. Continued research will clarify the pathogenesis of the disease processes and the mechanism of action of the targeted nutrients, both of which should improve clinical outcome, and provide an expanded role for nutrition in the management of trauma.

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