Nutrition and Inflammatory Events: Highly Unsaturated Fatty Acids (ω-3 vs ω-6) in Surgical Injury (43414)

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The account of acute inflammation is one of the classical clinical descriptions in medicine, dating back to Celsus' observation of "*rubor et tumor cum calor et dolor*" in 50 B.C. In healthy individuals, the response to tissue injury is often rapid and efficient. However, in malnourished patients, a complex series of events is set in motion, triggering the specific immune system (antigen-lymphocyte interaction), which can, in turn, affect nutrient substrate utilization and the metabolic response to inflammation. Thus, the primary goal of nutritional support for inflammatory disease is to provide adequate nutrients for tissue repair, to restore cellular function, to control the physiologic inflammatory response, and to prevent secondary infection.

Dietary fat has been shown to influence immune function by altering the fatty acid components of membrane phospholipids, which in turn significantly affects prostanoid metabolism. Evidence indicates that the biologically active metabolites resulting from the oxygenation of arachidonic acid (20:4ω6)—prostaglandin, thromboxane, and prostacyclin of the two-series—are associated with immunosuppression, including the inhibition of lymphocyte proliferation, cytokine secretion (i.e., interleukin (IL)-1 and IL-2, which in turn inhibits T cell function), macrophage collagenase synthesis, natural killer cell activity, and the tumoricidal activity of activated macrophages.

However, the potency of these 2-series eicosanoids can be modified by supplementing diets with fats low in linoleate content (e.g., coconut oil) or high in ω-3 polyunsaturated fatty acids (PUFA; e.g., fish oil). Eicosapentaenoic acid (20:5ω3) and docosahexaenoic acid (20:6ω3) in fish oil can partially antagonize the overproduction of eicosanoids derived from ω-6 PUFA by competing as a substrate for cyclooxygenase. In addition, these ω-3 PUFA produce biologically inactive metabolites of the 3- and 5-series that are less inflammatory. Finally, manipulating the fatty acid composition of dietary lipids may alter both the physical and biological properties of cell membranes, including fluidity, receptor binding sites, immunoresponsiveness to mitogens, and modulation of intracellular hormone action.

Continuous feeding with novel lipid formulations—ω-3 PUFA, medium chain triglycerides (MCT), γ-linolenic acid, structured lipids (fish oil/MCT)—may improve survival in patients in whom the inflammatory process threatens to cause irreversible damage, as in septic shock or endotoxemia. Animal studies have shown that fish oil can reduce response to endotoxin, thus protecting them from ensuing endotoxic shock and lactic acidosis, and that fish oil significantly lowers metabolic expenditure and improves cell-mediated immune response (demonstrated by lower adrenal weights and serum C3 levels), as compared with burned animals fed safflower oil. The use of MCT as part of structured lipids additionally avoids "clogging" the reticuloendothelial system and reduces the risk of hepatic dysfunction.

In both medical and surgical patients, novel lipids could, therefore, beneficially replace glucose calories to prevent cholestastis and hepatomegaly that may result from excessive carbohydrate feeding; based on current knowledge, optimal oxidative utilization of glucose, endogenous free fatty acids (preferred energy source of the liver), and exogenous lipid can be achieved by limiting glucose infusion to approximately the daily endogenous production rate of 3 g/kg/day. However, effective application of nutrition immunotherapy will require accurate monitoring of immune function in individual patients to avoid inappropriate therapy as suggested by studies of diabetes and hyperlipidemia.

Research to date provides the rationale for adjuvant therapies directed at altering host prostaglandin synthesis to modify a variety of clinical states. Future investigations must focus on the competition between ω-3 PUFA and ω-6 PUFA to favor the synthesis of less

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inflammatory eicosanoids, to promote immunomodulation, and to reduce platelet aggregation. Combined, the effects of dietary ω-3 PUFA in both institutionalized and free-living individuals should prove beneficial for altering several causes for mortality, including metastasis, immunosuppressive diseases, atherosclerosis, chronic inflammatory disorders, and other diet-related disease.

Nutrition and Inflammation: An Overview

While inflammation is most commonly associated with rheumatology, arthritis, and inflammatory bowel disease, it is the inflammatory events of acute, accidental, and surgical trauma that require and respond to nutritional modulation through use of foods for special medical purposes. Recovery from the latter trauma is conditioned by the process of inflammatory events due to their effect on wound healing and host defense against infection. We have reviewed previously the topic of diet, nutrition, and inflammation in an address in 1988 to the Nutrition Society (1) and will presently address the interactions between nutrition and inflammatory events related to acute, accidental, or surgical trauma.

Briefly, immunomodulation differs for the "hyper"-metabolic response (as in the development of acute lung injury) and the "hypo"-metabolic response (common in protein malnutrition and states of anergy). Furthermore, endotoxin secondary to hypotension and sepsis can activate leukocytes through oxygen free radical production, regional capillary ischemia, and reperfusion injury with peroxidation of highly unsaturated fatty acids. This exaggerated inflammatory response is potentiated through complex nonspecific and specific cell-cell interactions initiated by activated macrophages and natural killer cells. Major histocompatibility complex antigens on the surface of metabolically active cells promote allogenic rejection and endotoxemia related to cell-membrane injury and organ failure.

Cyclosporin, a unique immunomodulator, down-regulates response to major histocompatibility complex antigen-presenting cells and, when combined with mediation of prostaglandin synthesis by ω-3 PUFA, promises to be an adjunct therapy in critically ill patients (2). Hypermetabolic processes may also be modulated by γ-α-interferon, which inhibits B and T cell proliferation; low doses can stimulate the immune system primarily by increasing the cytotoxic activity of natural killer cells, macrophages, and T lymphocytes. Finally, malnutrition combined with immunosuppression may require nutrient strategies designed to enhance IL-1 production and lymphocyte proliferation through specific amino acid mixtures rich in arginine, branched chain amino acids, and perhaps glutamine. For example, feeding with up to 2% arginine has been shown to improve protein synthesis and to enhance immune function in burned guinea pigs (3).

Of course, the traditional goal of nutritional support has been to reduce nitrogen losses in stressed patients and, if possible, to achieve a positive nitrogen balance (with nitrogen balance acting as a surrogate for body cell mass). Increasingly sophisticated data have shown that immune dysfunction in critically ill patients is linked to metabolic deficiency and the acute-phase response to illness independent of any change in body cell mass (reflected by a wide range in nitrogen balance and/or loss, which is not sensitive to inflammation). Flow cytometric immunofluorescent methods involving monoclonal antibodies and lymphocyte surface markers have shown abnormalities among T lymphocytes (4), as well as decreases in antibodies and levels of IL-1 and IL-2 (5, 6). As addressed in this paper, metabolic substrates can have a profound effect on the immune system by direct and indirect mechanisms, and the battle against inflammation can be won through specialized, supportive feeding.

While successful nutritional immunomodulation requires careful attention to a wide variety of macro- and micronutrients (amino acids, carbohydrate, vitamins, and minerals), research has overwhelmingly pointed to the lipid source as a pivotal factor in reducing inflammation and enhancing immune response. In accidental or surgical trauma, inflammatory mediators, initiated by an endotoxin challenge (primarily from gram-negative bacteria), interact with IL-1 and tumor necrosis factor. Host defense against inflammatory events starts with cell-mediated immunity through the interplay between bacteria and antigen-presenting cells, such as the macrophage. The degree of cytokine (IL-1, IL-2, and tumor necrosis factor) production is then determined by the prostaglandins, of which leukotriene B_4 (from arachidonic acid) is an important factor. Other cells to target for special nutritional intervention include the natural killer cells and various cytotoxic T cells, such as the T helper inducer and suppressor cells. By manipulating the lipid used in the total parenteral nutrition solution, such as with a combination of ω-6 and ω-3 PUFA and MCT, the metabolism of individual cell activities can be altered in favor of host defense and survival (7).

Novel Lipids

Lipid emulsions made of microdroplets of long chain triglycerides (LCT) have been used extensively as a source of calories and of essential fatty acids for years. These microdroplets are filtered out of circulation by the liver, spleen, and lungs, where macrophages then phagocytose the fat. After 2 or 3 days, the macrophages become laden with fat droplets and their ability to remove microorganisms from the circulation is very much reduced (8, 9). This may cause bacteria from the gut to bypass the liver and become sequestered in the lungs, where they set up secondary inflammation and sequential organ failure (10, 11).

In seeking replacements for the ω-6 PUFA used in most fat emulsions today, researchers must examine closely the composition of the fatty acids: saturated (MCT in coconut oil), monounsaturated (ω-9 monounsaturated fatty acid in canola oil), and polyunsaturated (ω-3 PUFA, such as eicosapentaenoic acid in fish oil and ω-6 α-linoleic acid in safflower oil). Medium chain triglycerides, for example, can be absorbed into portal circulation and then metabolized by a hepatic oxidative process (12), even in patients with abnormal liver function and systemic sepsis. However, since the provision of some long chain triglycerides in the diet is essential, physical mixes of MCT and LCT have been administered to ameliorate the problems encountered with pure LCT (13).

Physical mixtures of MCT and LCT can be created through hydrolysis and random re-esterification (14) to produce structured triglycerides (ST) for optimal immunosupport. The resulting triglycerides consist of a glycerol backbone with variable-length fatty acid chains (15). The use of MCT and structured lipids together provides a method of caloric administration that will not "clog" the macrophages or cause hepatic dysfunction, thus avoiding the immunosuppressive effects of LCT alone. Through random esterification, investigators can select the best fatty acid, which will probably be in two monoglyceride fractions, that will provide the most specific and therapeutic solution. While such ST have not as yet been optimized, the basic science by which these synthesized lipids can be manufactured has been mastered. Our laboratory can now predict how varying concentrations of LCT (20–40%) and MCT (60–80%) will produce structured triglycerides with the desired number of long and medium chain triglycerides. The resultant mixture of ω-3, ω-6, and ω-9 fatty acids will favorably influence the balance of prostanoids, leukotrienes, and thromboxanes in the 2-series (ω-6) versus the 3-series (ω-3). Future investigations will also be needed to examine the potential role of γ-linoleic acid from primrose, black currant, and borage oils.

Clinically, then, total parenteral nutrition fat emulsions must be designed that can lower the arachidonic acid concentration in the immunosuppressed individual and thus favor production of eicosapentaenoic acid and decosahexaenoic acid so as to obtain more thromboxanes in the A_3 category and more 3-series prostaglandins. Current total parenteral nutrition solutions, which provide ω-6 PUFA, enhance arachidonic acid production, leading to high concentrations of leukotrienes in the B_4 category and more E_2 prostaglandins. After feeding ω-6 PUFA, an endotoxin challenge has been shown to produce dramatic changes in blood flow and hypoxia in the kidneys and liver. The same challenge presented after ω-3 feeding, however, demonstrated preservation of kidney, liver, and lung cell function due in part to the lack of fatty acid retention in the liver that would normally occur with vegetable oil feeding (16, 17). Indeed, with the rapid oxidation of the MCT and the low infusion rates of ST, we can avoid fat accumulation in the liver and its associated morbidity.

In our laboratory, studies have compared animals fed diets of rat chow (control), beef tallow, fish oil (ω-3 PUFA), or hybrid safflower oil (ω-9 PUFA) that, post-transplantation, do not receive cyclosporin (18). In looking at allograft survival, the ability of the ω-3 and ω-9 PUFA to serve as immune-sensitive lipids and hence to reduce rejection is clear: When low doses (to avoid associated toxicity) of cyclosporin are administered, the length of graft survival in those animals fed either fish or oleic vegetable oils is nearly doubled compared with those fed low-fat chow. Considering the few adjuvant therapies available for the promotion of allograft survival, the use of a special lipid diet offers much promise to liver, kidney, and heart-lung transplants.

Additional benefits of manipulating dietary lipids include the change in membrane phospholipid fatty acids, leading to improved fluidity and oxygen delivery and hence avoiding the hypoxia observed among tissues with high production of arachidonic acid E_2 prostaglandins, B_4 leukotrienes, and A_2 thromboxanes. Such nutritional immune therapy can also be used to influence macrophage antigen presentation; to correct the balance of T suppressor and T helper cells; to avoid the hyperimmune response to adult respiration distress syndrome; and to modify production of IL-1, IL-2, tumor necrosis factor, and γ-interferon. Of course, the individual organ that will best reflect the success of this therapy will be the liver (in the hepatocytes, Kupffer cells, and the entire reticuloendothelial system), though the lungs and kidneys will also respond significantly. The initial advantage will come from physical mixtures of MCT and various vegetable oils (the first choice being canola oil), but will quickly move on to customized structured lipids that utilize the benefits of both MCT and LCT. The use of novel triglycerides for special medical purposes has been reviewed extensively in recent years (19, 20).

Amino Acids, Nucleotides, and Carbohydrate

Investigations must, of course, examine the physiologic interactions between the lipid source and the nutritional solution's content of protein, glucose, xylitol, and micronutrients to identify properly the potential clinical benefit. Optimal solutions will incorporate new lipids (low in linoleic acid and high in fish oil, ST, and MCT) as well as mixtures of xylitol and glucose and of arginine and glutamine. Indeed, as we look to new amino acids to complement these novel lipids, branched chain amino acids should likewise be reconsidered for their therapeutic effect on insulin metabolism.

Among the amino acids, those most important in nurturing immune function are arginine, glutamine, and the branched chain amino acids as a group. Arginine, known to enhance immune function in both animal (21–23) and human studies (24), appears to have a direct effect on the thymus gland and T lymphocytes, which leads to enhancement of cellular immunity. This effect can benefit patients who have undergone a "stress" response, in which cellular immunity is depressed and thymic involution has occurred (25, 26). In addition, clinical trials with cancer patients have demonstrated improved immune function in those fed arginine (27).

Glutamine, although not routinely added to nutritional support prescribed for critically ill patients, appears to be the major amino acid lost during muscle proteolysis in the initial response to injury (28). Thus, negative nitrogen balance may be reduced significantly by glutamine administration. Enteral administration of glutamine has been shown to preserve and to improve muscle cellularity in the small and large bowel, and this improved condition may prevent the translocation of bowel organisms into the portal vein (29, 30). This effect would be particularly valuable in critically ill patients with an impaired intestinal mucosal barrier. Glutamine is also the preferred small bowel oxidative fuel (31).

Branched chain amino acids have been shown to improve whole-body protein synthesis and albumin renewal (32, 33), a critical feature for any nutritional support of immunodysfunction. The majority of present regimes contain 18–22% of their protein source as branched chain amino acids. Specifically, the acute-phase response to illness provides substrates for synthesis of proteins that enhance immunity (34, 35), as discussed earlier. The preferred source of energy during this process are branched chain amino acids, the major source of which is skeletal muscle. Thus, muscle wasting occurs in critically ill patients, which must be countered by appropriate nutritional support.

Recently, the importance of nucleotides, absent from most standard formulas used in tube feeding, has been appreciated (36, 37). Rapidly growing tissues, especially lymphoid cells and intestinal epithelium, require purines and pyrimidines either from the diet or from *de novo* synthesis in the liver (38). During critical illness, liver function may become impaired, placing greater dependence on exogenous sources of nucleotides. It may be that during illness, exogenous nucleotides will prove essential for the maintenance of cell-mediated immunity.

Amid exciting discoveries in lipid and protein metabolism toward immunotherapy, the former use of glucose as the primary energy source (especially when given above the endogenous production rate of 3 g/kg/day has been shown to induce cholestasis and hepatomegaly (from accelerated hepatic lipogenesis), as well as attenuated secretion of very low density lipoprotein triglycerides. With the advent of novel lipids, some glucose calories can be safely and effectively replaced by MCT and ST so as to promote normal liver function. Another option involves keeping the contribution of carbohydrate to total calories constant, but replacing more and more of the standard glucose with xylitol (39).

Micronutrients and Feeding Route

Finally, the response to inflammation involves increased utilization of trace elements, minerals, and vitamins. When a heightened need is compounded by decreased intake and increased losses, it is not surprising that deficiency of micronutrients is common in seriously ill patients (40). Zinc, for example, is a metallic cofactor for many enzymes, especially those involved in the synthesis of the acute-phase proteins (41). Deficiency markedly impairs the response to stress, with documented abnormalities including impaired platelet aggregation, defective chemotaxis, and delayed wound healing (42, 43).

Iron deficiency should also be avoided and corrected in ill patients, since iron is essential for hemoglobin synthesis, although high levels of free iron must be avoided because certain bacteria flourish in an iron-rich environment. Iron replacement must be approached with care, especially if levels of the transport protein transferrin are reduced (44).

One last category of micronutrients to address specifically are the antioxidants, a group of substances that have an affinity for oxygen free radicals. Peroxidative oxidation is a common final pathway in much of the tissue damage seen in intense inflammation and organ failure (45), and microvascular endothelial damage occurs as a result of released superoxides, as does hepatic mitochondrial and cell membrane damage. The administration of these free radical scavengers, including copper, vitamin E, and selenium, helps to protect vessels and organs from the ravages of excessive inflammation (46).

Aside from the actual components of nutritional support, the route of administration also plays a key role in outcome. Although many clinical situations demand parenteral nutrition, often enteral administration is not considered when, in fact, it would be appropriate. Moreover, evidence has shown that the capacity of the small bowel to absorb fluid and nutrients persists even in conditions of ileus (47, 48). Decreased nutrient intake increases the rate of bacterial translocation from the gut to the portal vein and favors bacterial overgrowth within the lumen (49), whereas administration of an oral diet stimulates B lymphocytes to produce secretory IgA, an important element of the intestinal mucosal barrier (50, 51). Appropriate enteral administration of fluids and nutrients may increase bowel capacity to withstand bacteria in the lumen. Patients should, therefore, be routinely assessed regarding their suitability for enteral feeding.

Summary

Given the poor prognosis and high cost of care for patients with acute inflammatory responses (often leading to organ failure and/or allograft rejection), immunomodulation of this hyperresponse represents an important priority for research in nutritional medicine. The primary goal of nutritional support in inflammatory disease is to provide adequate energy, particularly through use of novel lipids (to alter eicosanoid pathway toward a more regulated inflammatory state), and protein to meet endogenous requirements for tissue repair, IL-1 production, and restored cellular function, thus preventing secondary infection (52). Manipulation of macrophage eicosanoid production by use of ω-3 PUFA may reduce the cellular immune response (by competing with arachidonic acid, which produces inflammatory eicosanoids of the 2- and 4-series), whereas inclusion of MCT found in coconut oil may lower the arachidonic acid content of membrane phospholipids. As more data are obtained on the use of such tailored therapies in critically ill patients, a new generation of parenteral and enteral diets will be developed to reduce inflammation and immune dysfunction.

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