Dietary Treatment in Secondary Wasting and Cachexia

Bruce R. Bistrian

Laboratory of Nutrition/Infection and Division of Clinical Nutrition, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215

Protein calorie malnutrition (PCM) arising secondary to disease occurs in a spectrum that ranges from marasmus to cachexia to hypoalbuminemic malnutrition related to the relative role played by semistarvation and the systemic inflammatory response (Bistrian et al. 1974, Bistrian et al. 1976). Certain disease conditions involve principally semistarvation by three common mechanisms: (1) voluntary reduction of intake through primary eating disorders such as anorexia nervosa and bulimia nervosa or as a result of severe psychiatric disorders such as manic depressive illness; (2) reduction of intake due to the development of aversive symptoms on eating such as emesis with partial or complete gastrointestinal obstruction or diarrheal illness exacerbated by dietary intake from secretory diarrheas or malabsorption syndromes; and (3) short gut syndromes that lead to inadequate intestinal length or function following vascular thromboses, disease (Crohn’s Disease), surgery, or radiation.

When semistarvation is the principal mechanism for the development of PCM, a characteristic clinical picture is produced including weight loss, fat loss reflected in substantial loss of subcutaneous fat, and lean tissue loss, particularly of skeletal muscle, identified by a marked reduction in upper arm circumference, temporal muscle and generalized muscle wasting, but relatively good preservation of immune function and a normal serum albumin (Bistrian et al. 1977). Although such individuals tolerate the stress of injury or infection poorly unless there is exogenous provision of adequate quantities of all essential nutrients (Klein et al. 1997) there is little evidence to suggest an increased susceptibility to infection (Hoffman-Goetz et al. 1981). Most importantly, their response to complete nutritional support is excellent, with marked efficiency of protein utilization when protein intakes increase from the recommended dietary allowance (.8 g/kg) to high intakes (1.5 g/kg) and when energy intakes are increased from maintenance to surfeit (Shaw et al. 1983, Smith et al. 1977). The greatest concern in this setting is the refeeding syndrome which principally represents the multiple effects of hyperinsulinemia due to dietary carbohydrate, including enhanced antidiuretic, antiinflammatory, and anabolic effects that can precipitate congestive heart failure and potentially lethal hypototassemia, hypophosphatemia, and/or hypomagnesemia if dietary repletion is too aggressive (Apovian et al. 1990, Weinsier and Krumdieck, 1981).

At the other end of the spectrum is the PCM that results as a consequence of the systemic inflammatory response. The systemic inflammatory response principally derives through neuroendocrine mediation characterized by central regulation of mobilizing hormones, particularly catecholamines, glucagon, corticosterone, and growth hormone that serve to mobilize glucose, fatty acids, and amino acids from glycogen and protein, fat, and protein, respectively. A second major factor is the stimulation of cytokine production in numerous tissues, but principally arising from cells of the monocyte/macrophage line, on activation by a wide variety of stimuli including microorganisms (bacteria, fungi, protozoa, viruses), endotoxin, teichoic acid, various chemicals, complement and antigen-antibody complexes, cancer, and inflammatory, autoimmune, cardiac, and liver disease. Cytokines are intercellular messengers which have certain distinguishing features including small size (8-30 kilodaltons), activity in picomolar amounts, production by many different cells rather than specific organs, de novo production rather than release from storage in response to exogenous rather than endogenous stimuli, amplification through extensive cascades, and activity principally by autoimmune (on the same cell that secretes the cytokine), paracrine (on the neighboring cell), rather than through an endocrine (distant cell) mechanism (Dinarello 1984, Schwartz and Abraham 1996). There have been more than 20 cytokines described (Schwartz and Abraham 1996). Certain key points should be made regarding cytokine pathophysiology using sepsis as a model. The principal proximate cytokines are interleukin-1 (IL-1) and tumor necrosis factor (TNF) which orchestrate the panoply of responses in sepsis through effects on immunomodulation, vascular permeability, cardiac, renal, and pulmonary function and metabolic changes in protein, fat,


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carbohydrate, and energy metabolism. TNF induces IL-1 secretion and acts synergistically with IL-1 in many of its actions. IL-1 and TNF stimulate other cytokines in a cascade fashion which serves to dramatically amplify the systemic inflammatory response (Schwartz and Abraham 1996). For instance, interleukin-6 (IL-6) produces many of the same changes seen with IL-1 and TNF including fever, acute phase protein synthesis, cortisol production, and immune activation, while decreasing IL-1 and TNF production, whereas interleukin 8 (IL-8) leads to leukocyte recruitment and activation and has chemotactic activity (Schwartz and Abraham 1996). Many of the actions of cytokines are mediated through second messengers including eicosanoids (prostaglandins, prostacyclins, leukotrienes, thromboxanes), arachidonic acid, platelet activating factor, and nitric oxide, as well as the initiation of other systems including complement, coagulation, fibrinolytic, and kinin cascades. The cytokine cascade has both pro-inflammatory and anti-inflammatory components, with IL-1, IL-2, IL-3, IL-6, IL-7, and IL-8 being pro-inflammatory and IL-4, IL-6, IL-10, and transforming growth factor beta (TGF-B) being down regulators of inflammation (Schwartz and Abraham 1996). Interleukin-1 receptor antagonist (IL-1ra) is an agonist produced in conjunction with IL-1 stimulation which binds to IL-1 receptor but has no agonist action (Ling et al. 1995). Furthermore, shed receptors for TNF (p55 and p75), so-called soluble TNF receptors, are able to bind TNF in the circulation, rendering it inactive (Schwartz and Abraham 1996). A number of acute phase proteins also function as anti-inflammatory agents, including those with antiprotease, antioxidant, anticoagulant activity or the ability to bind pro-inflammatory cytokines. Several of the nonspecific effects of inflammation resulting from IL-1, TNF, or IL-6 action, such as the sharp fall in serum iron and zinc, have implications for immune function as well as for feeding the critically ill patient. Hypoferremia reduces the growth of many pathogenic bacteria (Weinberg 1984) and iron repletion during infection has been shown to increase morbidity and mortality (Murray et al. 1980, Weinberg, 1984). Recently, the administration of zinc in a total parenteral nutrition formula has been shown to exacerbate the inflammatory response in man (Braunschweig et al. 1997).

It becomes immediately apparent that such a finely tuned and highly orchestrated response that has persisted for the eons of human existence is likely to be beneficial under most circumstances, at least on a teleologic level. There is substantial evidence that abrogation of the systemic inflammatory response by a variety of anticytokine strategies, including anti-endotoxin, IL-1ra, and soluble TNF receptors has either not helped or worsened outcome in critically ill patients (Fink 1995). This is presumably because the cytokine cascade is helpful in most critically ill patients who are moderately stressed, at least initially before malnutrition supervenes, and only potentially more harmful than helpful in a very limited group of patients for some brief period of time. Two additional constraints to effective use of anticytokine therapy are (1) the very brief window of opportunity given the limited effectiveness when postexposure treatment is delayed and (2) the limited clinical ability to distinguish rapidly between the most severely ill, who might benefit from such therapy from the more moderately ill, who probably would not, to the least ill, who might well be harmed. In addition to the acknowledged role of cytokines in infections and sepsis (Dinarello 1984, Rixen et al. 1996), inflammatory cytokines have been shown to play major roles in trauma (Pullicino et al. 1990, Roumen et al. 1993), burns (Endo et al. 1996, Streiter et al. 1993), congestive heart failure (Endo et al. 1996, McMurray et al. 1991), chronic obstructive pulmonary disease (De Godoy et al. 1996), end-stage renal disease and dialysis (Pereira et al. 1994), chronic liver disease (McClain et al. 1993), the cachexia of chronic disease (Cederholm et al. 1997), AIDS (Bell et al. 1996), and at least some forms of cancer (Falconer et al. 1994). The principal distinguishing feature between cytokine involvement in severe injury (burns, trauma, sepsis, and severe infections such as malaria (Feuerstein et al. 1994), and meningococcemia (Jacobs and Tabor 1990)) and more chronic syndromes such as rheumatoid arthritis, chronic cachexia, AIDS, and cancer is that, in the former IL-1 and TNF can be identified initially in the systemic circulation (i.e., an endocrine response) due to the severity of the injury response that presumably involves a major contribution from the hepatic (Kupfer) cells, whereas in chronic illness only an enhanced release of IL-1, TNF, or IL-6 spontaneously or in response to stimulation in peripheral blood mononuclear cells tested in vitro, may be noted. A second major difference which has considerable relevance to feeding patients who manifest a systemic inflammatory response is that severe burns and trauma as well as many severe infectious illnesses are self-limited in duration or can be treated, thereby abrogating the nutritional consequences of the inflammatory response. For many chronic illnesses, although the nutritional consequences of inflammatory response are muted, they are often of extended duration and cannot be primarily removed. This is presumably the reason why a common pattern in the end stage of many chronic illnesses is unintentional weight loss and the development of severe PCM resistant to nutritional support (De Vys et al. 1980, Feld et al. 1984, Kotler et al. 1989, Marton et al. 1981).

This, then, represents the three basic types of PCM: marasmus, resulting principally from semistarvation; cachexia, development from a low level, long duration systemic inflammatory response; and hypoalbuminemic malnutrition arising as a consequence of severe injury or infection that is generally limited in duration. There is an additional important interaction between body composition and cytokine physiology. The marasmic form of PCM is characterized by relative preservation of immune function as assessed by delayed cutaneous hypersensitivity (Bistrian et al. 1977) or the production of cytokines by stimulated peripheral blood mononuclear cells (Hoffman-Goetz et al. 1981). With the hypoalbuminemic form of PCM, there is a dramatic reduction in cytokine production (Hoffman-Goetz et al. 1981, Keenan et al. 1982) and, thus an impaired ability to mount a systemic inflammatory response, which, however, can be rapidly restored by short-term nutritional repletion (Hoffman-Goetz et al. 1981, Keenan et al. 1982). This may account for the established efficacy of short-term preoperative nutritional repletion of malnourished patients to improve postoperative outcome as well as its demonstrated value in critical illness (Klein et al. 1997).

There are profound nutritional implications of the systemic inflammatory response. First and foremost is the impact on protein metabolism. PCM occurs as a consequence of cytokine production by four principal mechanisms. Both IL-1 and TNF produce profound anorexia and thus semistarvation (Ling et al. 1996, 1997). Secondly, illness (cytokines) produces a profound reduction in voluntary motor activity which leads to muscle wasting. Thirdly, cytokines reduce the rate of muscle protein synthesis (Flores et al. 1989) and increase the rate of muscle protein catabolism (Istfan et al. 1991, Young et al. 1983). Only the anorexia-induced semistarvation can be totally overcome by invasive feeding. The net protein catabolism from inactivity and basic disturbances in muscle protein.
components of lean tissue in addition to nitrogen (e.g., potassium) and the maintenance of homeostasis, particularly glucose homeostasis (Pomposelli and Bistrian 1994) and acid-base balance (Reaich et al. 1995), there remain two important components of lean tissue restoration for which there are no answers—only interesting and intriguing research opportunities. The role of resistance training to improve lean tissue accretion in the setting of illness is just beginning to be explored (Ferrando et al. 1997). The role of anabolic agents, including appetite stimulants like tetrahydrocannabinol (Struewe et al. 1993) and postgestational agents (Von Roenn et al. 1994), anabolic agents such as growth hormone (Shambelen et al. 1996), insulin-like growth factor-1 (Waters et al. 1996) and androgens (Grinspoon et al. 1996, Mendenhall et al. 1993), and anticalcitol agents like pentoxifylline (Landman et al. 1994) and thalidomide (Makikawkeyoon et al. 1993) is being tested principally in AIDS with, at most, mild success. There is a possibility that cytokine blockade with agents like IL-1β (Ring et al. 1995) or soluble TNF receptors (Kelly et al. 1996) might be effective in some dose that could improve anabolic efficiency while not impairing the immune benefits of cytokines. However, it seems theoretically more logical to attempt to identify a more distal agent in the cytokine cascade that affects protein synthesis and/or catabolism but not the more beneficial components of the systemic inflammatory response. However, we have been somewhat thwarted in this process by the failure to identify the actual cytokine that is active directly on the skeletal protein turnover. A final form of therapy that warrants consideration is the use of nutritional compounds that can modulate the systemic inflammatory response such as omega-3 fatty acids (Kenler et al. 1996, Wigmore et al. 1996) or influence nitrogen metabolism like glutamine (Dickerson et al. 1986) to name but two among many possible avenues of approach. However, in the final analysis, there is little convincing evidence that our present methods of nutritional support, when correctly applied to critically ill patients in acute care hospitals who suffer from PCM of the hypoalbuminemic variety due to trauma, burns, or severe sepsis, are not able to accomplish the principal short-term goals of supporting immune function and fostering healing even though lean tissue repletion is generally not possible during the acute phase of injury. It appears that after a certain amount of lean tissue is lost after acute injury, there is a greater avidity for protein which prevents further lean tissue loss among the critically ill when adequate nutrition is provided save for the occasional patient with severe lung impairment and PCM who cannot be weaned from artificial ventilation. The far more common presentation of the irreversible development of PCM with chronic illness due to the ongoing inflammatory response to various chronic diseases including AIDS, cancer, or end-stage organ dysfunction is the focus of much interest, since it is certainly possible that if nutritional repletion were achievable, an improved quality of life and, potentially, an extended duration of life, would be feasible. There are also, however, likely to be other end-stage chronic conditions where one might only achieve the former or neither, since, in many instances, patients die with PCM rather than of PCM at all times in certain diseases, and at certain times in many different conditions. This entire area requires much more formal study, since, although it is a reasonable hypothesis that all PCM should be corrected, if and when possible, there is ample reason to suspect, based on clinical experience with other life-threatening illnesses, that this may not always be the case.

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