Metabolic Considerations in Management of Surgical Patients

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KEYWORDS

• Stress response • Metabolic response
• Surgery • Injury • Trauma

Surgical procedures are followed by prompt changes in endocrine metabolic function and various host defense mechanisms.[1] These physiologic shifts must be quickly addressed (within 24–48 hours) to avoid the pathogenesis of postoperative morbidity. The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system.[2] The overall metabolic effect of the hormonal changes is increased catabolism. This hormone-mediated mobilization of endogenous substrates provides energy sources, mechanisms to retain salt and water, and the means to maintain fluid volume and cardiovascular homeostasis. The net effect is an increased secretion of catabolic hormones.[3] Rather than pathogenic, however, the stress response to injury should be viewed as a finely tuned, integrated series of compensatory reactions that provide adequate quantities of fuel and amino acids for visceral protein synthesis.[4,5]

METABOLIC RESPONSE TO INJURY

History

In 1932, Sir David Cuthbertson[6] described the metabolic responses of four patients with lower limb injuries by documenting the time course of the changes. Ten years later, he was the first to describe distinct phases of the metabolic shifts that occur after major trauma by characterizing the ebb and flow of posttraumatic metabolic alterations.[7,8] The ebb phase is associated with a decline in body temperature and oxygen consumption, presumably aimed at reducing posttraumatic energy depletion. The clinical relevance of this phase is limited by its brevity. Conversely, the flow phase takes place after resuscitation from a state of shock.[9] It involves sustained

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hypermetabolism for at least 7 days and, in many severely injured patients, up to 3 weeks or longer.[10,11] This hypercatabolic condition leads to significantly increased oxygen consumption and energy expenditure—a state associated with severe complications related to hyperglycemia, hypoproteinemia, and immunosuppression.[4,9,12]

Dr Francis D. Moore was a pioneer in the field of metabolic responses to surgery. His studies culminated in two classic books, *The Metabolic Response to Surgery* coauthored with M.R. Ball[13] and *Metabolic Care of the Surgical Patient*.[14] These shifted the focus from improving the surgical craft to understanding the body's physiologic response to the trauma of surgery. Surgeons of the day did not understand how to optimize the physiologic status of their patients. A perfect anatomic operation could be followed by disastrous complications or death from a low level of circulating sodium chloride or magnesium, a high level of potassium chloride, or an undetected loss of plasma or water.

Dr Jonathan E. Rhoads at the Harrison Department of Surgical Research, University of Pennsylvania, focused on nutrition in surgical patients. He discovered that providing 100 g of glucose enables the body to draw on stores of fat for the remaining caloric supplement and promoted 100 g of protein as a stopgap measure. His work led to the later demonstration that an intravenous nutrient mixture could support normal growth in young animals and in children with severe bowel disease who received no food by mouth.[15]

Rhoads' younger colleague, Dr Stanley J. Dudrick,[16] invented total parenteral nutrition through the development of intravenous hyperalimentation and then advanced the clinical utility of surgical nutrition and its successful application in critically ill patients. In 1967, he demonstrated that a human infant could receive all nutrients entirely by intravenous feeding and still grow and develop normally. This seminal accomplishment, published in *JAMA*, laid the groundwork for many improvements in the technique and its further development and application. At a reception for the second Jonathan E. Rhoads Lectureship at the meeting of the American Society for Parenteral and Enteral Nutrition in 1979, this was the first time Dr Rhoads met Sir David Cuthbertson (**Fig. 1**).[17]

Stress Catabolism

Surgical trauma initiates a complex series of metabolic host responses designed to maintain homeostasis and ensure survival.[18] Hormone-mediated mobilization of endogenous substrates (**Fig. 2**) leads to a functional redistribution of body cell mass after injury or surgery to provide nitrogen for protein synthesis. Catecholamines (epinephrine), corticosteroids, glucagon, and growth hormone mobilize stored protein and energy reserves in support of key pathways necessary for metabolic stabilization, host defense, and recovery. Free fatty acids, ketones, and glucose meet energy needs, whereas amino acids are used for the synthesis of acute phase proteins, gluconeogenesis, and thermogenesis essential for the homeostasis of injury metabolism.[4,9,12]

This initial period is characterized by increased oxygen consumption, insulin resistance, and protein catabolism. Modest hyperglycemia is common due to increased hepatic glucose production and peripheral insulin resistance in skeletal muscle.[19] Changes in lipid metabolism include increased lipolysis, fatty acid recycling, hypertriglyceridemia, and hepatic steatosis.[20] Postinjury metabolism is further characterized by increased skeletal and visceral muscle catabolism and negative nitrogen balance. This leads to depletion of lean body mass, a syndrome referred to as autocannibalism.[21] Glutamine released from muscle becomes the preferred energy substrate for enterocytes and immune cells and is used to synthesize the antioxidant glutathione.[22] Hepatic protein synthesis is prioritized to generate acute phase proteins

Fig. 1. (*Left to right*) Dr Jonathan E. Rhoads, Sir David Cuthbertson, and Drs George L. Blackburn, William Steffee, and Stanley Dudrick. Reception for the second Jonathan E. Rhoads Lectureship at the third meeting of the American Society for Parenteral and Enteral Nutrition at the Massachusetts Room, Harvard Club, Boston (1979). This was the first time Dr Rhoads met Sir David Cuthbertson. (*Courtesy of* George L. Blackburn, MD, PhD, Boston, MA.)

(eg, C-reactive protein) and immune cells (eg, leukocytes and neutrophils) at the expense of constitutive proteins, such as albumin.[23–25]

These metabolic changes are best understood as a redistribution of macronutrients from labile reserves (skeletal muscle and adipose tissue) to more active tissues (liver and bone marrow) for host defense, visceral protein synthesis, and heat production

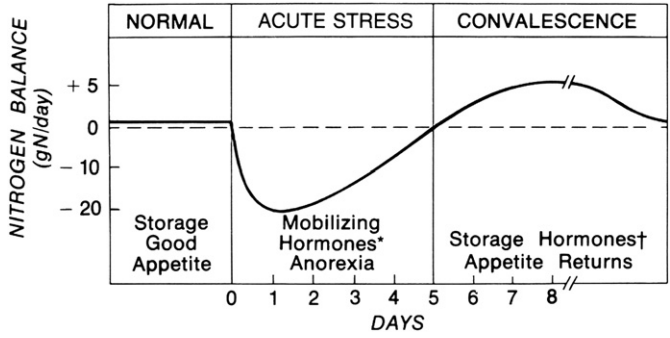

Fig. 2. Biphasic hormonal response to injury in the normal postoperative patient. Catecholamines*, cortocosteroids, glucagon, growth hormone, injury hormones, leukocytic mediators, storage hormones, insulin†. (*From* Blackburn GL, Harvey-Wilkes KB. Nutrition in surgical patients. In: Hardy JD, editor. Hardy's textbook of surgery. 1st edition. Philadelphia: J.B. Lippincott; 1983. p. 90–107; with permission.)

(Fig. 3). Micronutrients are also redistributed. The liver increases uptake of zinc, which is a cofactor in several enzymatic functions required during and after injury. Greater amounts of iron are also taken up by iron-binding proteins, such as transferrin, thus reducing the amount available for iron-dependent pathogenic microorganisms.[4]

NEUROENDOCRINE RESPONSE TO INJURY

Stress Hormones

Injury is associated with a pronounced neuroendocrine response characterized by increased secretion of various stress hormones, such as adrenaline and cortisol, but also by increased release of glucagon, growth hormone, aldosterone, and antidiuretic hormone.[26,27] The magnitude and duration of the hormonal response correlate well with the extent of the trauma.[28] Afferent impulses from the site of injury stimulate the secretion of hypothalamic-releasing hormones that further stimulate the pituitary gland.[29] Cortisol is secreted by hormonal stimulation of the adrenal cortex, whereas adrenaline in secreted by the adrenal medulla in response to activation of the sympathetic nervous system. Noradrenaline spills over into the plasma from the sympathetic nerve endings.

From a metabolic standpoint, cortisol is probably the most important hormone, with its widespread effects on glucose, amino acid, and fatty acid metabolism. No evidence to date shows that hormonal treatment can improve the outcome after major

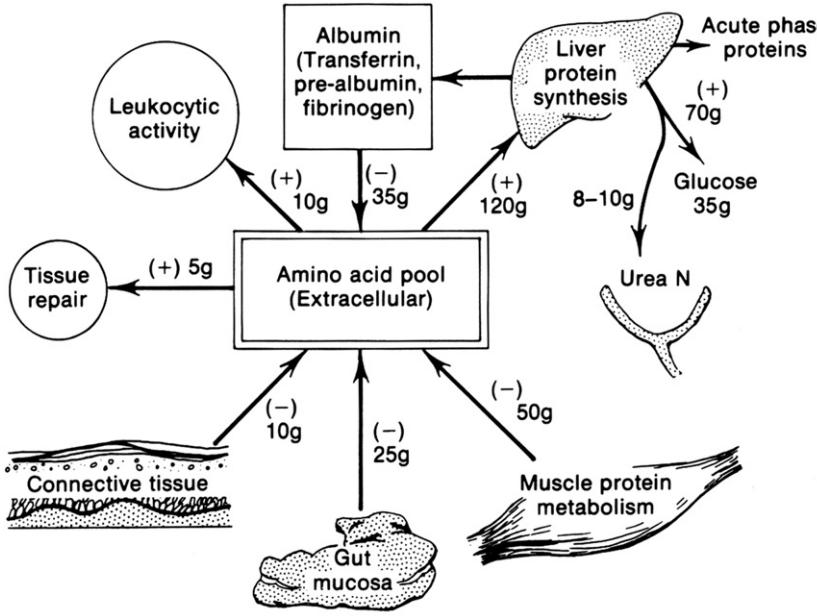

Fig. 3. Functional redistribution of body cell mass after injury or surgery provides nitrogen for protein synthesis. Arrows reflect the net release (−) in grams from connective tissue, gut mucosa, and muscle as well as uptake (+) of amino acids into tissues whose net metabolism is associated with survival. The conversion of protein into glucose and urea is a minor source of energy but an important part of the role of the liver to produce the heat necessary to maintain core temperature. (*From* Blackburn GL, Harvey-Wilkes KB. Nutrition in surgical patients. In: Hardy JD, editor. Hardy's textbook of surgery. 1st edition. Philadelphia: J.B. Lippincott; 1983. p. 90–107; with permission.)

trauma in humans,[29] although promising experimental trauma research has been performed suggesting some potential modulating effects on the response.[30]

Cytokines—Host Defense

Considerable evidence indicates that infections occur more frequently, and with greater severity, in malnourished individuals. The immune system, however, encompasses a wide variety of host defenses and activities—phagocytosis, antibody synthesis, lymphokine production, complement-mediated cytolysis, interferon production, and sirtuin substrate actions.[31] These functions require the interaction of 3 types of leukocytes: thymus-derived (T), antibody synthesizing (B) lymphocytes, and accessory cells (eg, monocytes/macrophages, neutrophils, and endothelium).[9] Many cooperative interactions and activities depend on protein synthesis.

Nutritional depletion from anorexia, increased metabolic rate, malabsorption, or increased losses (fistulas and diarrhea) may compromise immunocompetence. Therefore, a variety of cytokines come into play when prompted by an inflammatory stimulus. The most widely studied proinflammatory cytokines with respect to metabolic regulation after injury, inflammation, and infection are tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6. Other cytokines that may be involved in the metabolic response to injury and infection include IL-4, IL-7, IL-8, and interferon-γ (IFN-γ). This list will probably grow longer as new cytokines and their functions continue to be identified. Known cytokines and additional ones, along with their functions, origin, target cells, and properties are provided in the Cytokines Online Pathfinder Encyclopaedia.[32]

The IL-6–type cytokines, TNF-α, and IFN-γ,[33] are released in response to tissue injury or an inflammatory stimulus. They act locally and systemically to generate a variety of physiologic responses, in particular, the acute phase response. The IL-6 cytokines demonstrate pleiotropy and redundancy of actions.[34]

Different proinflammatory cytokines induce the activation of leukocytes. The leukocyte adhesion molecule, L-selectin, is important for the rolling of polymorphonuclear leukocytes (PMN), the first step of the cascade leading to adhesion, diapedesis, and subsequent organ dysfunction.[35] Mommsen and colleagues[35] recently found that the primary proinflammatory cytokine TNF-α regulates the L-selectin surface expression on PNM after surgical trauma, suggesting that a regulation of neutrophil adjustment on this level might be crucial in the development of posttraumatic complications. In this immune phase of the inflammatory response, the metabolic response to injury is characterized by hypercatabolism and hypermetabolism.[29,36–39]

The Hormone-Cytokine Connection

Neuroendocrine stress reactions interact with the immunologic response to trauma.[40] The immunoinflammatory response is initiated immediately after injury and is mainly regulated by cytokines, which act as communication mediators between leukocytes, bridging the innate and adaptive immune responses.[41,42]

Evidence shows that hormones and cytokines interact at several levels in the regulation of the metabolic response to surgery. For example, TNF-α, IL-1, and IL-6 stimulate the hypothalamus-pituitary-adrenal axis. In normal human subjects, TNF-α administration induces a stress hormone response with elevated plasma levels of corticotropin, cortisol, catecholamines, growth hormone, and glucagon.

Corticotropin-releasing factor, which is released from the hypothalamus during stress, is produced by leukocytes as well.[43] Immune cells are also considered a new, diffusely expressed adrenergic organ, with the ability to generate, release,

and degrade catecholamines.[42] It seems that catecholamines use intracellular oxidative mechanisms to exert autoregulatory functions on immune cells.[44]

The physiologic counterpart of the adrenergic system, the cholinergic system, is also an integral part of human macrophage and lymphocyte regulation, and is termed the *cholinergic anti-inflammatory pathway*.[42]

IMMUNOLOGIC ASSAYS

Experienced clinicians are unable to predict the extent to which trauma or injury will affect an individual's energy requirements.[45] Immunologic assays are valuable for assessing the functional and clinically significant severity of malnutrition. Simple measurements include an enumeration of total leukocytes (ie, total lymphocyte and neutrophil counts). Decreased lymphocyte counts (<1000 m^3) have been seen in hypoalbuminemic postsurgical patients and children with kwashiorkor but not in those with marasmus. Rapid protein depletion due to increased protein catabolism may have a different effect on immune response than the more gradual generalized depletion from anorexia and inadequate protein and carbohydrate intake. Other explanations for decreased leukocyte counts might include factors, such as blood loss, white blood cell migration to traumatized tissues, and cell sequestration in lymphoid tissues.[4]

The nonspecific immune defense systems—in particular, complement and immunoglobulin—are the primary mechanisms for containing bacterial contamination and preventing colonization, infection, and sepsis. Because complement and immunoglobulin synthesis have a high priority with respect to amino acid availability, they are not useful in the detection of mild or moderate nutritional deficiency in hospitalized patients. In cases of severe protein-calorie malnutrition, however, such as that seen in burn patients, decreased complement and immunoglobulin levels may become evident.

Delayed hypersensitivity skin testing, which evaluates cell-mediated immunity, is the most widely used assay for the analysis of immune function before elective surgery or before and during nutritional support (**Fig. 4**). A positive skin test requires functioning accessory cells, T and B lymphocytes, macrophage activation, lymphokine production, and monocyte chemotaxis. A wide variety of metabolic systems can interfere with this complex process. Anergy has been reported not only in immune deficient states but also in advanced age, uremia, bacterial and viral infections, and liver disease. Transient anergy often follows surgery or acute injury and is due to the appearance of a serum inhibitor or to T-lymphocyte reactions. One should, therefore, wait until the seventh or eighth postoperative day before evaluating the delayed hypersensitivity reaction.[4]

Radiation and chemotherapy, as well as cancer itself, may also act to depress the DH response to recall skin antigens. Thus, protein-calorie malnutrition is not the only cause of acquired anergy in the hospitalized patient. But regardless of the etiology, depression of cell-mediated immunity (as reflected by delayed hypersensitivity skin antigen testing) has been associated with increased sepsis and related mortality. This is so even though those organisms, against which cell-mediated immunity is not the primary host defense, are frequently the cause of the sepsis.

In most patients, the infectious agents are gram-negative rods or gram-positive cocci, ubiquitous organisms generally from a patient's own flora, rather than viruses, fungi, or intracellular parasites from the environment. In healthy, well-nourished individuals, indigenous flora are normally of low virulence. One possible mechanism for the increased incidence of sepsis associated with anergy is that the critical number of bacteria that ordinarily expected to be handled by the inflammatory response may be altered. DH testing does not identify the deficit; it is simply a marker that the immune system is not functioning adequately.

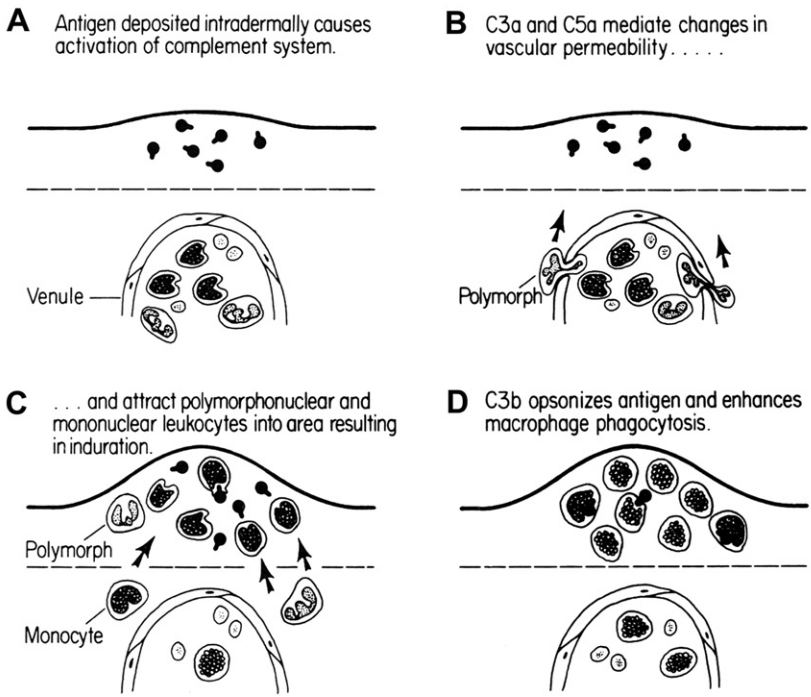

Fig. 4. Delayed hypersensitivity skin testing, which evaluates cell-mediated immunity, is the most widely used assay for the analysis of immune function before elective surgery or before and during nutritional support. (*From* Blackburn GL, Harvey-Wilkes KB. Nutrition in surgical patients. In: Hardy JD, editor. Hardy's textbook of surgery. 1st edition. Philadelphia: J.B. Lippincott; 1983. p. 90–107; with permission.)

Because of their high metabolic priority, immune functions of lymphocytes or accessory cells may be the first metabolic system to respond to nutritional support; thus, serial measurements of immune function may be of use to determine the appropriateness and effectiveness of nutritional therapy. Serial measurements are also valuable predictors of outcome (eg, mortality) in hospital therapy.

To measure the intactness of the delayed hypersensitivity response, 3 recall skin antigens—*Candida albicans,* mumps, and streptokinase-streptodornase—are commonly used. One-tenth milliliter of each solution is placed intradermally in the volar forearm, and the reaction is examined at 24 hours and 48 hours; a greater than or equal to 5-mm area of induration is considered positive. Immune competence is defined as a positive response to one or more of the antigens. Ninety-five percent accuracy of the test can be anticipated if it is meticulously performed. Although a negative response to recall skin antigen (in particular, mumps and *Candida*) may be due to a variety of causes, a positive serial response can provide important knowledge about the integrity of the host defense system and the effectiveness of nutrition support therapy—parenteral, enteral, or a combination of the two methods.[4]

TRANSCRIPTION FACTORS

Transcription factors are proteins that under certain conditions bind to DNA and alter the rate of gene transcription and expression. They may enhance gene transcription,

resulting in increased mRNA levels and, ultimately, upregulated protein expression. Alternatively, they may serve as repressors and inhibit gene transcription, thus decreasing production of a given protein. Examples of important transcription factors involved in the inflammatory response to injury and sepsis include nuclear factor κB (NF-κB), activating protein 1 (AP-1), signal transducer and activator of transcription factor (STAT)-3, and members of the CCAAT/enhancer-binding protein (C/EBP) family of transcription factors, in particular, C/EBPβ and C/EBPδ. Because of their key roles in gene regulation and as potential targets for treatment of inflammation, transcription factors have become subjects of intense scientific investigation. NF-κB is probably the most extensively studied inflammatory transcription factor, and is, therefore, discussed briefly.

A recent experiment in an animal model showed that the transplantation of mesenchymal stem cells modulated the inflammatory response to injury by neutralizing the activity of inflammatory cytokines. The study suggested that improvements in inflammatory responses in animal models after local transplantation of mesenchymal stem cells are explained, at least in part, by the NF-κB–dependent secretion of soluble TNF receptor 1 by mesenchymal stem cells.[46] Another experimental study found that activation of peroxisome proliferator-activated receptor -γ (PPARγ) seemed to play an important role in mediating salutary effects of 17β-estradiol on plasma cytokine levels and Kupffer cell cytokine production after trauma. PPARγ and Kupffer cell cytokine production are likely mediated via NF-κB and AP-1.

NF-κB is a redox sensitive transcription factor with regard to the production of proinflammatory molecules, including chemokines, cytokines, and adhesion molecules, that allow leukocytes to attach themselves to the endothelium and facilitate their extravasation to the interstitial spaces of tissues and organs.[47,48] The NF-κB family of proteins consists of several members, including p50, p52, c-Rel, p65 (Rel-A), and Rel-B. Each of these subunits can form homodimeric or heterodimeric complexes with other members of the family. Several other transcription factors also participate in gene regulation after trauma and during severe infection, including AP-1, STAT-1, hypoxia-inducible transcription factor, and C/EBPβ and C/EBPδ. In addition, new insights into the genetic response to inflammation may provide assays, potential biomarkers, or therapies, such as histone deacetylase inhibitors, that promote tissue repair while preventing inflammation from becoming chronic.[49–51]

ENERGY EXPENDITURE AND PROTEIN REQUIREMENTS

Energy Expenditure

The average nonstressed individual lying quietly in bed requires 23 kcal/kg per day to maintain body weight. Limited physical activity increases this requirement to 28 kcal/kg per day.[52,53] Ordinary, uncomplicated, open abdomen elective surgery does not lead to a significant increase in energy requirements. Increased metabolic response and protein catabolism result from the release of cytokines combined with more secretion of catabolic hormones.[54] This creates a heightened caloric requirement secondary to the catabolic response in severely injured or septic patients. Needs are increased approximately 25% in skeletal trauma, 50% in sepsis, and 75% to 100% in severe burns (**Fig. 5**).[55] Hypermetabolic patients are also subjected to an increased drain on protein stores. The following nitrogen losses are commonly seen in fasting patients: elective postsurgical patients, 7–9 g N per day; skeletal trauma or septic patients, 11–14 g N per day; severe burns, 12–18 g N per day.

Monitoring of nitrogen excretion is a simple, accurate assessment of the catabolic rate.[12] Assessment of body mass can be determined by the creatine index.[56] The

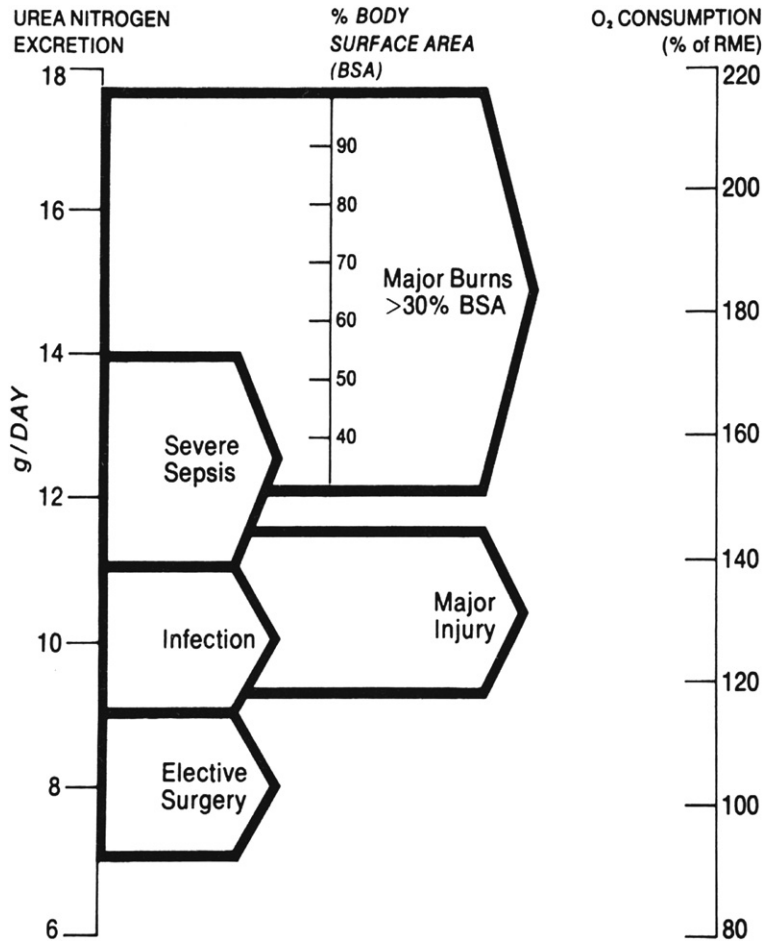

Fig. 5. Rates of hypermetabolism estimated from urinary urea nitrogen excretion. (*From* Blackburn GL, Bistrian BR, Maini BS, et al. Nutritional and metabolic assessment of the hospitalized patient. JPEN J Parenter Enteral Nutr 1977;1:11–22; with permission.)

addition of exogenous corticosteroids to the high circulating levels characteristic of stress can increase nitrogen losses even further.

Hypocaloric nutrition support offers another approach to meeting the energy needs of patients with evidence of accelerated gluconeogenesis and lipolysis that lead to hyperglycemia and elevated serum triglyceride levels.[57] In some cases, the traditional strategy of meeting or exceeding calorie requirements may compound the metabolic alterations of the stress response.[57] Increasing evidence suggests that critically ill patients have lower energy requirements than expected, but most guidelines[25,58] continue to recommend elevated caloric requirements in these patients, in particular those with sepsis.[59] This practice can lead to liver dysfunction.[59]

Most critically ill patients show an average resting energy expenditure of 23 kcal/kg^{-1}/d^{-1} before and during total parenteral nutrition, close to their total daily energy expenditure (without differences between septic and nonseptic patients).[60,61]

Although inconclusive, studies suggest that a nutrition support goal of 10 to 20 kcal/kg of ideal or adjusted weight and 1.5 to 2 g/kg ideal weight of protein may be beneficial during the acute stress response.[57]

Protein Requirements

Protein catabolism is stimulated by increased cortisol concentrations. Predominantly, skeletal muscle is broken down, but some visceral muscle protein is also catabolized to release the constituent amino acids. The amino acids may be further catabolized for energy or used in the liver to form new protein, in particular acute-phase proteins. The liver also converts amino acids into other substrates (eg, glucose, fatty acids, or ketone bodies). Protein catabolism results in marked weight loss and muscle wasting in patients after major surgical and traumatic injury. The loss of protein can be measured and calculated indirectly by increased nitrogen excretion in the urine.

Both hormones and cytokines regulate protein metabolism after injury. The hormonal regulation may reflect a balance between catabolic hormones, such as glucocorticoids, and anabolic hormones, such as insulin and insulinlike growth factor 1. During trauma and infection, both types of hormones probably play a role in protein regulation. The role of the various mediators in protein metabolism after injury has been most extensively studied in skeletal muscle and liver, although evidence is emerging that the same substances regulate protein metabolism in other organs and tissues as well.[62]

Much interest has been shown in nutritional supplements for patients with critical illness and those undergoing major surgery. Certain nutrients may have a beneficial influence on the immune status of stressed patients. Glutamine, arginine, glycine, ω-3 polyunsaturated fatty acids, and nucleotides have been studied most extensively.[2] Glutamine and arginine are semiessential amino acids with a multiplicity of functions, including stimulation of immune activity. Studies of patients given enteral nutrition supplemented with arginine or glycine after major surgery have shown that patients benefited with a faster recovery of immunologic parameters, fewer infectious complications, and a shorter hospital stay.[3]

SUMMARY

The stress response consists of the hormonal and metabolic changes that follow injury or trauma. It is part of the systemic reaction to injury,[62,63] which encompasses a wide range of endocrinological, immunologic, and hematological effects.[2,64] The endocrine response to surgery affects the hypothalamic-pituitary-adrenal axis. For example, surgery is one of the most potent activators of corticotropin and cortisol secretion; increased plasma concentrations of both hormones can be measured within minutes of the start of surgery.[2]

The metabolic sequelae of the endocrine response center around increased secretion of catabolic hormones. Surgery affects metabolism of carbohydrates, protein, fat, and water and electrolytes.[2] Most critically ill patients have evidence of an increased metabolic response and protein catabolism that results from the release of cytokines combined with increased secretion of catabolic hormones.[54,59] With prolonged stress and catabolism, substrate levels (in particular amino acids) fall, resulting in decreased synthesis of plasma proteins, especially those concerned with host defense. For clinical purposes, a 5-day rule is an important marker, indicating the time that supplemental nutrition support should begin to sustain the metabolic response to injury without development of malnutrition and risk of impaired host defense and wound healing.[2,4,65]

Early observations by Cuthbertson confirmed that severe injury initiated systemic catabolic responses and eventually enabled him to assign a causal association between this response and the increased presence of the stress hormones, catecholamines, and glucocorticoids. Today we know that the stress response encompasses a wide range of endocrinological, immunologic, and hematological effects. A variety of approaches have been used to attenuate the stress response and improve outcomes.[66] Reducing the trauma associated with surgical illness has decreased morbidity and mortality and has made significant contributions to improved outcomes in surgical patients. Further advances in these approaches will continue to enhance surgical care in the future.[65,67–69]

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