

Cachexia

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Cachexia represents the clinical consequence of a chronic, systemic inflammatory response, and its manifestations differ considerably from those of starvation. Although cachexia is classically associated with chronic infections and malignant conditions, some of its elements have been identified in a wide variety of chronic diseases and in aging persons. Cachexia has repeatedly been associated with adverse clinical outcomes. The changes seen in cachexia are multidimensional and highly coordinated. Most obvious is a redistribution of the body's protein content, with preferential depletion of skeletal muscle and an increase in the synthesis of proteins involved in the response to tissue injury—the so-called acute-phase response. The physiologic, metabolic, and behavioral changes of cachexia are tightly regulated by cytokines, which signal the synthesis of acute-phase proteins as well as

changes in intermediary metabolism that provide substrate and energy. The metabolic adaptations, notably the increase in the rate of protein degradation, limit the ability of hypercaloric feeding to reverse the depletion of lean mass. Recent studies have demonstrated the ability of anabolic and anticatabolic agents to mitigate the loss of skeletal muscle and to improve clinical outcomes in selected circumstances. Preclinical initiatives target the cytokine regulation of protein metabolism. It should be stressed that metabolic manipulation in cachexia could have positive or negative clinical effects, which must be distinguished through appropriate clinical trials.

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Cachexia is a classic clinical phenomenon that evokes historical images of sickbeds and patients with “consumption.” A physician's first experience with a cachectic patient may be memorable, if indescribable. Steady progress by a generation of investigators has increased our understanding of cachexia, which has evolved from phenomenology to fundamental human biology. Cachexia is now seen as a multidimensional adaptation encompassing a variety of alterations that range from physiologic to behavioral (Table 1). Adverse consequences of cachexia have been documented in patients with cancer (1), congestive heart failure (2), AIDS (3), and other diseases. The presence of cachexia also confounds attempts at nutritional support through hypercaloric feeding.

Despite long and widespread interest in the topic, there is no standard definition for cachexia, which means simply “poor condition” in Greek. Accelerated loss of skeletal muscle in the context of a chronic inflammatory response is a characteristic feature of cachexia and will be considered its definition in this review. Many chronic or end-stage diseases, such as infections, cancer, AIDS, congestive heart failure, rheumatoid arthritis, tuberculosis, chronic obstructive pulmonary disease, cystic fibrosis, Crohn disease, and others, demonstrate some nutritional changes of cachexia. Cachexia may develop in a proportion of elderly persons without obvious disease. Even pure starvation may evolve to cachexia in clinical situations because malnutrition-induced immune dysfunction predisposes to infection.

A literature search using the term *cachexia* yielded 785 articles published over the past 5 years. Those that appeared in English-language journals were scanned and analyzed for common and novel themes. This review discusses recent advances in the understanding of selected aspects of cachexia, including changes in body composition, food intake, intermediary metabolism, energy balance, cytokine regulation, the spectrum of clinical diseases, and recent therapeutic initiatives (both clinical and preclinical).

PARADIGMS OF MALNUTRITION

Cachexia and starvation are the two major paradigms of malnutrition. Starvation is characterized by pure caloric deficiency. The organism adapts metabolically to conserve lean mass and increase fat metabolism (4), and the changes can be reversed by appropriate feeding. Intestinal disease with malabsorption is a form of starvation characterized by excess fecal losses of ions and water, in addition to nutrients. In contrast, cachexia is associated with inflammatory or neoplastic conditions that evoke an acute-phase response, and feeding does not reverse the macronutrient changes. A third paradigm of malnutrition is sarcopenia (5), which is characterized by subnormal contents of skeletal muscle in the absence of weight loss. The term *sarcopenia* is most commonly used to refer to body composition changes in elderly persons but can also apply to patients who have repeatedly tried to lose weight by dieting, patients with growth hormone deficiency, and patients with

Table 1. Adaptations Associated with Proinflammatory Cytokines

Behavioral/conscious
Anorexia
Fatigue
Malaise
Altered sleep pattern
Altered level of consciousness
Physiologic
Increased body temperature
Increased resting energy expenditure
Stress hormone response (cortisol, epinephrine, glucagon)
Skeletal muscle wasting
Increased hepatic acute-phase response
Trace mineral sequestration
Decreased gastric emptying, intestinal transit
Bone marrow suppression
Diuresis
Nutritional
Weight loss
Negative nitrogen balance
Hypoalbuminemia
Hyperinsulinemia
Hypertriglyceridemia
Hypocholesterolemia, low levels of high-density lipoprotein cholesterol

very limited physical activity, such as those debilitated by painful arthritis. Clinically, the situation may be complicated because cachectic patients are often anorectic and others may have sarcopenia.

DETECTION OF MALNUTRITION

The diagnosis of malnutrition is complicated because nutritional alterations may involve macronutrients or micronutrients and the depletion may be stable or progressive. Most clinicians rely on body weight as the major measure of nutritional status, using usual adult weight as a reference. The range of body weight is wide, even when normalized by height (body mass index), but the range of individual weight fluctuations over time is much narrower. Rosenbaum and colleagues (6) showed that the 95% CIs for change in body weight in healthy adults were approximately $\pm 2\%$ in 1 month, $\pm 3.5\%$ in 3 months, $\pm 5\%$ in 6 months, $\pm 10\%$ in 1 year or after up to 5 years of follow-up, and $\pm 20\%$ after more than 5 years of follow-up (Figure). Rates of change beyond these limits can be considered abnormal. However, rates of change within these limits may also be abnormal if divergent changes are seen in different body compartments (for example, depletion of skeletal muscle plus fluid overload caused by cardiac, hepatic, or renal disease; hypoalbuminemia; or intravenous hydration). In addition, measurement of weight cannot

differentiate between lean tissues or fat, and, as noted, some debilitated patients have sarcopenia (5). Because of these limitations, nutritional analysis is now done by using body compartment analysis, a process in which fat is distinguished from fat-free mass and fat-free mass is further separated into body cell mass and extracellular mass.

CHANGES IN BODY COMPOSITION IN PATIENTS WITH CACHEXIA

Moore and coworkers (7) reported the results of body composition studies in healthy persons, obese persons, and persons with acute and chronic injury. The studies they examined were performed by using isotope dilution techniques during the first 20 years after World War II. The authors showed that patients with cachexia lose roughly equal amounts of fat and fat-free mass but maintain extracellular water volume. Losses of fat-free mass are centered in skeletal muscle and reflect decreases in both cellular mass and intracellular potassium concentration; the latter indicates a bioenergetic deficit.

Many clinical studies have corroborated the findings of Moore and coworkers in patients with cancer (8), AIDS (9), congestive heart failure (10), end-stage renal disease (11), rheumatoid arthritis (12), and other conditions. Weight loss is common but not universal. Experimental studies have used the technique of pair-feeding to distin-

Figure. Ninety-five percent CIs for weight change in healthy adults studied twice after variable time intervals (adapted with permission from Rosenbaum and colleagues [6]).

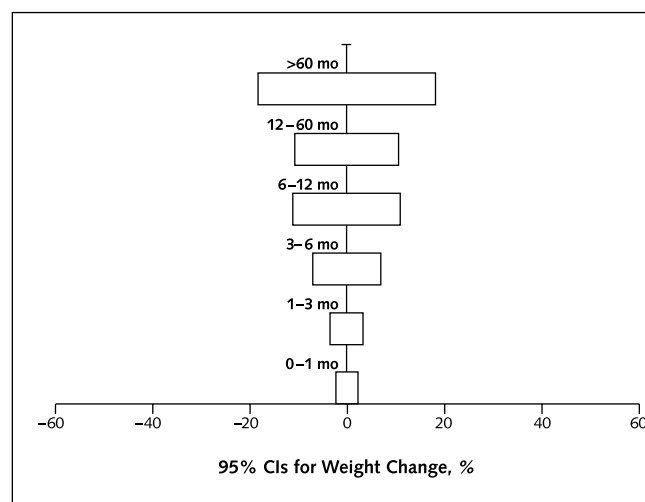


Table 2. Nutritional Alterations in Starvation and Cachexia*

Variable	Starvation	Cachexia
Body weight	—	0/—
Body cell mass	—	---
Body fat	---	---
Caloric intake	---	---
Total energy expenditure	---	—
Resting energy expenditure	---	++
Protein synthesis	---	+/-
Protein degradation	---	+++
Serum insulin	---	+++
Serum cortisol	0	++

* Minus sign = decrease; plus sign = increase; 0 = no change.

guish cachexia from starvation. Studies that provide a control group with a hypocaloric diet matching the level of anorexia seen in cachectic animals have shown that loss of skeletal muscle cannot be attributed simply to decreased food intake. In muscle loss, pale fibers are affected more than red fibers and predominantly myofibrillar proteins are involved, as shown by measurements of 3-methylhistidine (13). Visceral protein synthesis, unlike skeletal muscle, increases in cachexia (14).

Several factors, including the patient's sex, may influence changes in body composition. Studies in HIV-infected persons have demonstrated that women lose more fat than lean mass (85% vs. 15%), whereas men lose roughly equivalent amounts of both (15). The cause for this dimorphism is uncertain but could be related to the different physiologic effects of male and female sex hormones. Forbes (16) showed that the composition of weight change is significantly related to baseline body composition; higher fat contents lead to greater losses of fat regardless of the cause. Since healthy women have more body fat than men, these results may partly explain a sexual dimorphism in the composition of weight loss.

PATHOGENESIS OF CACHEXIA

Tissue damage is a threat to well-being because it is self-promoting; that is, hydrolases released from inflammatory or injured cells cause further injury and provide substrate for formation and propagation of free radicals. For this reason, the body must localize and limit the injury and clear tissue debris. To perform these functions, the organism has developed an acute-phase response that includes stereotyped, coordinated adaptations ranging from behavioral to physiologic (17) (Table 1). The acute-phase re-

sponse includes the hepatic synthesis of large quantities of proteins. The functions of the acute-phase proteins vary widely and include binding proteins (opsonins), protease inhibitors, complement factors, apoproteins, fibrinogen, and others. For example, a cycle involving C-reactive protein, complement, and interleukin-6 has been described (18). C-reactive protein, which was named for its ability to bind to a specific bacterial lipopolysaccharide, circulates in low quantities in healthy persons; however, its levels increase in response to inflammatory or neoplastic processes. C-reactive protein is an opsonin that binds to denatured proteins, lipopolysaccharides, and nucleic acids. Binding leads to local complement activation and phagocytosis by macrophages through their complement receptors. The complement-split products stimulate release of interleukin-6 by macrophages, which in turn stimulates the synthesis and secretion of more C-reactive protein in the liver. This completes a positive feedback loop. The intensity of this response is quantitatively related to the amount of tissue debris; the response extinguishes itself after tissue debris is cleared.

The acute-phase response has nutritional implications. It is energy-intensive with high rates of hepatic protein synthesis and requires large quantities of essential amino acids. The need for essential amino acids drives the loss of skeletal muscle. The survival value is obvious: An injured animal has an impaired ability to obtain exogenous protein, and skeletal muscle, which represents approximately 40% of body weight in men and approximately 33% in women, is the largest available pool of protein. The tradeoff may be viewed as a shift in the body's priorities from offensive to defensive. The adaptation is effective over the short term because skeletal muscle is replaced rapidly as recovery is completed. Problems ensue when the process is chronic because skeletal muscle depletion contributes increasingly to morbidity and mortality.

CHANGES IN INTERMEDIARY METABOLISM DURING THE ACUTE-PHASE RESPONSE

The acute-phase response includes coordinated adaptations in intermediary metabolism, which differ from those of starvation (Tables 2 and 3). A major difference is an increase in protein degradation in skeletal muscle. Recent studies have partially defined the mechanisms by which cellular protein turnover is regulated. Turnover rates vary for individual proteins. Regulatory proteins, such as

those that control the cell cycle, have extremely rapid turnover; for others, such as myofibrillar proteins in skeletal muscle, turnover is slower. Of the various cellular proteolytic pathways, the adenosine triphosphate-dependent ubiquitin–proteasome pathway has the predominant role in the regulation of protein turnover (13). This proteolytic pathway has great specificity and adaptability. Proteins to be degraded are marked by covalent binding to a small protein, ubiquitin. They are then transported to a barrel-shaped molecule, the 26S proteasome, within which proteolysis occurs. The proteasome structure is designed to avoid nonspecific protein digestion. Selectivity in the rate of protein degradation occurs at the level of ubiquitin binding and transport proteins. Under normal circumstances, the activity of this pathway is stimulated by glucocorticoids and thyroid hormone and is inhibited by insulin. The ubiquitin–proteasome pathway is the mediator of protein degradation in cachexia (13). Several proinflammatory cytokines, including tumor necrosis factor (TNF) and interleukin-1, stimulate production of ubiquitin messenger RNA (mRNA).

Cachexia is also characterized by changes in fat metabolism, including hypertriglyceridemia, increased hepatic secretion of very-low-density lipoproteins, decreased lipoprotein lipase activity, increased de novo triglyceride synthesis and esterification, increased release of free fatty acid from the periphery, and a futile cycle of fatty acids between the liver and adipose tissue beds. These changes, which are promoted by a variety of cytokines, maintain serum lipid concentrations despite the presence of anorexia (19). There is no clear link between hypertriglyceridemia and progressive weight loss in infection or cancer. An intriguing hypothesis is that hyperlipidemia is linked to host defense rather than to nutritional status and is part of innate rather than adaptive immunity. Survival benefit was demonstrated in a mouse model of endotoxin-induced death, in which human lipoproteins and soy-based lipid emulsions were protective (20). Absorption into circulating lipoproteins may increase the hepatic clearance of microbial compounds, including bacterial lipopolysaccharides and enveloped viruses, with subsequent lysosomal degradation (21).

Alterations in carbohydrate metabolism include peripheral insulin resistance, which is also mediated by proinflammatory cytokines. This adaptation redirects glucose to the liver and other viscera and away from skeletal muscle because hepatic glucokinase is not affected by insulin, unlike hexokinase in myocytes and elsewhere. The energy

Table 3. Metabolic Alterations in Cachexia

Protein
Increased urinary nitrogen loss
Increased protein turnover
Decreased skeletal muscle protein synthesis
Increased skeletal muscle protein breakdown
Increased hepatic (acute-phase) protein synthesis
Decreased plasma levels of branched-chain amino acids
Lipid
Increased lipolysis
Decreased lipogenesis
Hyperlipidemia
Increased free fatty acid turnover
Decreased serum lipoprotein lipase activity
Increased de novo fatty acid synthesis
Carbohydrate
Glucose intolerance
Hyperinsulinemia
Insulin resistance
Increased glucose turnover
Increased gluconeogenesis

needs of muscle are met by oxidation of nonessential amino acids, which contributes to negative nitrogen balance.

ALTERATIONS IN ENERGY BALANCE IN PATIENTS WITH CACHEXIA: ANOREXIA COMPARED WITH HYPERMETABOLISM

Hypermetabolism, defined as an elevation in resting energy expenditure, is a cardinal feature of cachexia but not of starvation (Table 2). It was commonly believed that hypermetabolism is the direct cause of weight loss in cachexia. Several recent studies using two experimental approaches have successfully challenged that notion. In the first approach, statistical comparisons of correlations among resting energy expenditure, food intake, and weight changes are made. Studies in HIV infection (22, 23) and Crohn disease without malabsorption (24), among other diseases, showed that short-term weight change is more closely related to decreased caloric intake than to increased resting energy expenditure. In the second approach, total energy expenditure was measured by using the doubly-labeled water technique. Total energy expenditure involves resting energy expenditure (approximately 70%), voluntary energy expenditure (25%), and energy expended in digestion (5%). Studies in congestive heart failure (11), chronic obstructive pulmonary disease (25), and HIV infection (23) all showed that weight loss was associated with a decrease in total energy expenditure despite an elevation in resting energy expenditure. This is accomplished by a decrease in voluntary energy expenditure, which manifests

clinically as apathy and lethargy. The decrease in voluntary energy expenditure, although very significant clinically, does not compensate quantitatively for the combined increase in resting energy expenditure and decrease in caloric intake.

CYTOKINE REGULATION OF THE ACUTE-PHASE RESPONSE

The realization that the response to illness and injury is an endogenous, not exogenous, process was a milestone in the understanding of cachexia. Our understanding that cytokines regulate the acute-phase response and cachexia resulted from several observations. For example, studies of hypertriglyceridemia in experimental infections suggested indirect, or endogenous, control; the degree of hypertriglyceridemia was not necessarily correlated with infectious or tumor burden, and metabolic effects of infection could be reproduced with dead organisms or even with supernatants of macrophage cultures stimulated *in vitro*. The responsible protein was sought, isolated, and named *cachectin*, and its sequence was found to be identical to that reported for TNF (26). These studies concluded that this molecule was the mediator of cachexia.

At approximately the same time, other investigators demonstrated that proteolysis in animals occurred after infusion of a leukocyte-derived factor (27), in keeping with the notion of an endogenous mediator of the acute-phase response (28). This mediator was found after diverse stresses, ranging from vaccination to sepsis. The circulatory nature of a cachectic factor was shown by using parabiotic rats—that is, animals grown with a surgically produced, shared vascular supply. Cancer implanted in one rat led to anorexia and cachexia in both rats (29). Analysis of the components of leukocyte endogenous mediator yielded interleukin-1 and other proinflammatory cytokines. Further studies have shown that many cytokines are capable of inducing metabolic changes (19), although some specificity among cytokines can be demonstrated by using experimentally altered animal models.

Proinflammatory cytokines are protein mediators that are secreted from immunocompetent cells and other cells and that mediate the acute-phase response, among other functions. As noted, metabolic effects of cytokines can be distinguished from those of starvation by pair-feeding. One implication of combining immunologic and nutritional signal functions within a single molecule is that the inten-

sity of the nutritional adaptation parallels the other cytokine effects. Most experimental work has concentrated on TNF, interleukin-1, and interleukin-6, although other cytokines and chemokines also mediate the acute-phase response. The mode of action is predominantly paracrine and autocrine. A series of animal studies demonstrated that the predominant cytokine effect is local: Central infusion of TNF led to predominant anorexia, and peripheral production of TNF produced predominant metabolic losses of protein (30).

Cytokines do mediate systemic effects, however. Of the proinflammatory cytokines, interleukin-6 has the longest serum half-life and may have important endocrine effects. Circulation of mononuclear cells that secrete cytokines in a target organ is an alternate way to achieve a classic endocrine effect. Such a mechanism might be especially important in transmission of cytokine signals through the blood–brain barrier.

Proinflammatory cytokines exert a variety of behavioral and physiologic effects in addition to their immunologic and nutritional functions. Anorexia results from proinflammatory cytokine activity and has both central and peripheral elements. The central effect is at the level of the hypothalamic nuclei, which control feeding behavior. Several cytokines affect food intake directly or through other mediators, such as corticotrophin-releasing hormone, serotonin, or leptin. Leptin, a cytokine secreted from adipocytes that has prominent effects on feeding behavior and energy balance, is believed to be a major peripheral regulator of long-term body composition. It is also thought to be responsible for self-correcting changes in energy intake and expenditure that can be demonstrated after voluntary overfeeding and underfeeding (31). However, animal studies demonstrated that endotoxin leads to a dose-dependent increase in plasma leptin and white fat leptin mRNA (32–34), which implies that leptin might be a mediator of anorexia in cachexia. There is a normal relationship between plasma leptin concentration and body fat content in healthy persons as well as in patients with AIDS, cancer, and chronic obstructive pulmonary disease (35–39). Leptin does not mediate the metabolic changes of the acute-phase response (40).

Several alterations in gastrointestinal function that indirectly affect nutritional status have been ascribed to proinflammatory cytokines, including altered gastric emptying. Decreases in intestinal blood flow, changes in small

bowel motility, changes in cellular proliferation, and altered ion fluxes have also been described.

CACHEXIA IN CLINICAL DISEASES

A broad spectrum of clinical disease fits this paper's definition of cachexia. Cachexia due to cancer or infection has been recognized for many years. Recent studies have demonstrated elements of the acute-phase response of various types of cancer, including cancer of the pancreas, stomach, prostate, esophagus, and colon and rectum (41–47). In cancer cachexia, levels of fibrinogen, an acute-phase reactant (48), were elevated; levels of albumin synthesis, however, were not (49). These elevated levels of fibrinogen are associated with shortened survival (50). Cachexia in cancer may be due to endogenous or tumor-associated factors. Several laboratories have extracted lipid or protein-mobilizing factors from tumors (51, 52).

Infection with HIV and AIDS are also characterized by cachexia. Early studies of body composition demonstrated depletion of body cell mass (9). Metabolic alterations include elevations in resting energy expenditure and changes in lipid metabolism (53). Endocrine alterations include hypogonadism in both men and women (53), consistent with a hypoanabolic state (54, 55). Many studies have documented cytokine activation and its association with malnutrition (56) in HIV-infected persons. Studies of protein turnover demonstrate elevated plasma glutamine concentration as well as leucine oxidation in patients with weight loss, implying increased protein breakdown (57, 58). A poor response to hypercaloric feeding in patients with AIDS, in which fat accumulation occurs without changes in lean mass, is also consistent with cachexia.

Rheumatologic disease is a useful model with which to study cachexia associated with chronic inflammation. Depletion of body cell mass has been reported in patients with rheumatoid arthritis, who also have increased resting energy expenditures. Malnutrition in rheumatic disease increases morbidity. Studies of peripheral blood mononuclear cells from patients with rheumatoid arthritis showed increased release of TNF and interleukin-1 *in vitro* (12) that was linearly associated with resting energy expenditure. Energy intake was inversely related to interleukin-1 production (59) in an animal model of inflammatory arthritis.

Cardiac cachexia is a classic clinical entity that is seen in about 20% of patients with congestive heart failure (60)

and is an independent risk factor for death (2). Resting energy expenditure is elevated in cardiac cachexia (61) and is associated with decreased calculated voluntary energy expenditure but not total energy expenditure (10). Several studies found significant associations among circulating proinflammatory cytokines, or their soluble receptors, and cardiac cachexia (62, 63). In one study, detection of soluble TNF receptor was associated with poor survival (63). Changes in oxidative stress (64), blood flow, and bone mineral (65) are also associated with circulating cytokines.

Malnutrition is common in end-stage renal disease (11), in which depletion of skeletal muscle mass may be masked by an increase in total-body water volume. Malnutrition in end-stage renal disease is associated with increased mortality rates (66). Anorexia is a prominent clinical symptom. However, decreased albumin synthesis in patients with end-stage renal disease was inversely correlated with serum concentrations of the acute-phase reactants α_2 -macroglobulin and C-reactive protein. These correlations were stronger than the correlation with dietary protein intake (67). In addition, metabolic acidosis, which is prominent in end-stage renal disease, increases protein degradation as well as degradation of essential branched-chain amino acids, which prevent adaptation to decreased protein intake.

Malnutrition can be documented in up to 50% of patients with chronic obstructive pulmonary disease, in whom circulating TNF levels are associated with unintentional weight loss independent of measures of pulmonary function (68). Although patients with this disease may have a low caloric intake, increased breathing difficulty also contributes to malnutrition (69).

Malnutrition is a serious problem in elderly persons. Weight loss and hypoalbuminemia are more frequently associated with adverse outcomes than chronologic age is (70). Aging is associated with progressive increases in serum levels of glucocorticoids and catecholamines and decreases in levels of growth hormone and sex hormones. Elevated levels of proinflammatory cytokines may also be found. In one study of aging persons, serum levels of interleukin-6 were significantly associated with serum concentrations of C-reactive protein (71).

A few studies have identified cachexia in other diseases, such as alcoholic hepatitis, chronic pancreatitis, cystic fibrosis, and active inflammatory bowel disease. A recent study of children with protein energy malnutrition dem-

onstrated proinflammatory cytokine activity (72), possibly as a result of infectious or other complicating factors.

TREATMENT OF CACHEXIA

Appreciation of the potential benefits of nutritional therapy for cachexia varies widely among caregivers as well as the lay public. At one end of the spectrum are those who believe that all outcomes follow the course of the primary disease process and see no reason for intervention to maintain nutritional status. At the other end are those who pay great attention to nutritional details, at times to the exclusion of primary therapy. The proper role of nutritional and other complementary therapies lies somewhere between these extremes. As noted above, starvation and cachexia are overlapping but independent phenomena. Decreased physical activity may exacerbate the loss of skeletal muscle through deconditioning. The changes are presumably additive and provide rationale for the use of hypercaloric feeding and exercise to treat the changes of cachexia. Until recently, few published clinical studies of nutritional therapies have been designed to critically evaluate treatment effects for relevant, measurable clinical benefits.

Hypercaloric Feeding

The inability of hypercaloric feeding to increase lean mass, and especially skeletal muscle mass, has been shown

Table 4. Therapies for Cachexia

Hypercaloric feeding
Appetite stimulants
Megestrol acetate
Medroxyprogesterone
Dronabinol
Anabolic agents
Recombinant human growth hormone
Testosterone
Anabolic steroids
Resistance exercise training
Anti-inflammatory agents
ω -3 fatty acids
Cytokine inhibition
Pentoxifylline
Thalidomide
Antioxidants
Melatonin
Medroxyprogesterone
Megestrol acetate
Δ -9-tetrahydrocannabinol
L-Carnitine
Erythropoietin*

* Available for clinical use or undergoing clinical trials.

Table 5. Potential Therapies for Cachexia*

Cytokine inhibition
Antisense therapy directed at nuclear factor- κ B
Anti-interleukin-6 receptor antibody
Anti-tumor necrosis factor antibody
Soluble tumor necrosis factor receptor
Metabolic regulators
Insulin-sensitizing agents
β -Adrenergic agonists (clenbuterol)
Lipoprotein lipase activators (benzofibrate)
Serotonin type 3 receptor antagonists (ondansetron)

* All therapies are in preclinical stages of development.

repeatedly. Plank and colleagues (73) repeatedly studied body composition in critically ill patients over 3 weeks after the onset of peritonitis and found a 20% loss of lean body mass despite aggressive caloric supplementation. Older studies of hypercaloric feeding by total parenteral nutrition in patients with AIDS (74) and lymphoma (75) showed that weight gain may occur but leads almost solely to fat accumulation. The reason for this outcome is that the increase in protein degradation in cachexia is greater in magnitude than the possible increase in protein synthesis during hypercaloric feeding. However, some studies document objective benefits of caloric feeding on certain end points, which suggests that poor food intake and metabolic alterations may have independent adverse effects on outcome.

Appetite Stimulants

Appetite stimulants are an alternative way to increase caloric intake and are better tolerated than tube feeding, especially in an outpatient ambulatory setting. Megestrol acetate promotes caloric intake in patients with cancer (76) and HIV infection (53). However, the increase in weight is due to increases in fat, not fat-free mass (53, 77). Tetrahydrocannabinol has also been evaluated for its ability to stimulate appetite and promote weight gain. Dronabinol was significantly less effective than megestrol acetate in a comparative study in HIV-infected persons (78).

If feeding alone is insufficient to replete lean mass, then pharmacologic or other means are required. At present, few therapies have proven nutritional benefit in patients with cachexia. Clinical and experimental therapies can be divided into those available clinically and those whose efficacy is hypothetical and whose supporting studies are preclinical (Tables 4 and 5).

Anabolic Therapies

The most logical pharmacologic therapy for cachexia is an agent that promotes protein synthesis or inhibits protein breakdown. Both approaches have been tried. Recombinant human growth hormone was shown to promote nitrogen retention in short-term studies of HIV infection and lean mass accrual in a double-blind, placebo-controlled clinical trial; in the latter, functional improvement was also shown (79). The use of growth hormone to mitigate losses of lean mass during acute illnesses in patients with AIDS has been reported (80). In contrast, improvements in lean mass without concomitant functional improvements were seen in sarcopenia associated with aging (81) and in chronic obstructive pulmonary disease (82). Growth hormone has also been applied in patients with cardiomyopathy (83–85). Although use of growth hormone in patients with cancer is worrisome because of a theoretical positive anabolic effect on the tumor itself, the results of an animal study demonstrated that its combination with protein restriction led to increased growth of skeletal muscle at the expense of the tumor (86). Use of growth hormone could have a negative effect in some situations by diverting excess essential amino acids and energy to skeletal muscle and away from use in the acute-phase response, thereby thwarting a basic function of host defense. This situation could explain the substantial increase in mortality rates reported with use of growth hormone in critically ill patients (87). There is no evidence that concomitant administration of growth hormone with insulin-like growth factor I or other agents improves its effectiveness.

The other major anabolic agents available for clinical use are the anabolic steroids. Their application in clinical medicine has been impeded because they have frequently been used “off-label” to enhance physical performance or to produce cosmetic effects; in addition, few well-designed studies have proved their safety and efficacy. However, their use is being increasingly studied. In a small randomized trial of patients in the recovery phase after 30% to 50% full-thickness burns, Demling and DeSanti (88) showed that oxandrolone (20 mg/d) plus high protein intake and active physical therapy doubled weight gain compared with a treatment program that lacked the anabolic agent. An increasing number of studies are evaluating the use of testosterone and anabolic steroids in HIV-infected patients and have shown increases in fat-free mass (89–94).

Anabolic steroids have been widely used in end-stage renal disease because of their documented effects on eryth-

ropoiesis; in addition, they increase renal release of erythropoietin and increase protein synthesis in hematopoietic cells. Gaughan and coworkers (95) showed that the combination of erythropoietin and nandrolone increased hemoglobin concentration more than erythropoietin alone. Johansen and colleagues (96) demonstrated that nandrolone decanoate significantly increased fat-free mass compared with placebo and baseline levels. Changes in body composition were associated with increased oxygen consumption and increased work output on exercise testing. In contrast, anabolic steroids increased lean mass but not exercise tolerance in malnourished patients with chronic obstructive pulmonary disease (97), possibly because of limitations in tissue oxygen delivery. Positive effects have also been reported with the use of oxandrolone in patients with alcoholic hepatitis (98). Those studies also demonstrated strong associations between shortened survival and the extent of malnutrition, as well as the severity of liver disease.

Exercise Training

Several studies have evaluated resistance exercise training in various clinical diseases, among them rheumatology, HIV infection, and others. Nutritional benefits have been documented in patients with congestive heart failure (99) and HIV infection (100). Benefits have been reported for combination therapy in elderly patients (resistance exercise training and growth hormone) (101) and HIV-infected patients (resistance exercise training and anabolic steroids) (102).

Anticytokine Therapies

The other means of improving protein balance is through the inhibition of protein breakdown. However, it must once again be noted that excess breakdown of skeletal muscle protein may be life-sustaining in cases of serious acute illness or injury. Inhibition of proinflammatory cytokine activity can be shown to decrease protein breakdown *in vitro*. Some agents in current use have anticytokine properties *in vitro*, including the appetite stimulants megestrol acetate, medroxyprogesterone, and Δ^9 -tetrahydrocannabinol (103). Pentoxifylline has documented anti-TNF effects, although no significant beneficial effects have been seen in clinical studies. Thalidomide has been evaluated for nutritional benefits related to its anti-inflamma-

tory properties, which may be due, at least in part, to an increase in the degradation rate of TNF mRNA. Adjunctive use of thalidomide in HIV-infected patients receiving treatment for tuberculosis has been shown to promote weight gain (104, 105). Academic interest in the use of antioxidants in many diseases has recently increased; in addition, antioxidants have been shown to limit protein losses in experimental models of cachexia (106).

Anti-Inflammatory Agents

Anti-inflammatory therapies are an alternative way to moderate proinflammatory cytokine activity, since signal transduction may involve arachidonic acid metabolites. Lundholm and coworkers (107) showed that indomethacin and prednisolone maintained Karnofsky index and prolonged survival compared with placebo in patients with cancer cachexia. A combination of megestrol acetate and indomethacin led to accrual of fat (but not lean tissue) and decreased C-reactive protein concentration in patients with cancer cachexia (108). In another study, anti-inflammatory agents plus erythropoietin improved nutritional status, blood counts, and exercise capacity (109). ω -3 fatty acids have been proposed as therapy for cachexia because of their ability to alter cytokine release; in addition, they have had documented physiologic effects in animal and human studies (110). However, these benefits in cancer are not uniform in the literature. Anti-inflammatory agents may have a greater impact in nonmalignant cachectic conditions, such as rheumatologic diseases.

Preclinical Initiatives

Several novel approaches to the treatment of cachexia are in preclinical, animal phases of testing. Several varieties of cytokine inhibition are being evaluated, including an antisense sequence to nuclear factor- κ B, which binds to the promoter region of DNA and slows transcription of cytokine mRNA (111), anti-interleukin-6 receptor antibodies (112, 113), anti-TNF antibodies (114), and soluble TNF receptors (115). Melatonin is another compound that has been found to downregulate TNF production with the possibility of efficacy in clinical situations. The goal of mitigating the effects of TNF or other proinflammatory factors must be tempered by the fact that these responses may be life-sustaining and that excess inhibition could have harmful consequences.

A diverse group of metabolic regulators have shown

promise in preclinical studies, including insulin-sensitizing agents, which antagonize the effects of TNF at a cellular level (116); the β -adrenergic agonist clenbuterol (117), the hypolipidemic agent bezafibrate (118); and a novel activator of tissue lipoprotein lipase (119). L-Carnitine has been shown to have physiologic effects on metabolism in cachexia models, presumably because of its ability to increase fatty acid oxidation (120). Antagonists to the serotonin type 3 receptor are being evaluated as appetite stimulants because serotonin is associated with anorexia in cachectic animals. In patients with metastatic disease who were not undergoing chemotherapy or radiation therapy, ondansetron improved appetite but did not reverse weight loss or decreases in midarm circumference (121).

CONCLUSION

Ultimately, the strongest predictor of outcome is the severity of the underlying illness. Advances in prevention and treatment of the primary disease may improve overall health but are not likely to abolish cachexia. Further understanding of the mediators of cachexia, especially at the molecular level, will guide the development of treatment strategies. The development of nutritional therapies will continue and will be aimed increasingly at the preservation of skeletal muscle mass and functional capabilities. More widespread application of nutritional therapies will require demonstration of their safety and efficacy.

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