

Cachexia: pathophysiology and clinical relevance^{1,2}

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ABSTRACT

Cachexia causes weight loss and increased mortality. It affects more than 5 million persons in the United States. Other causes of weight loss include anorexia, sarcopenia, and dehydration. The pathophysiology of cachexia is reviewed in this article. The major cause appears to be cytokine excess. Other potential mediators include testosterone and insulin-like growth factor I deficiency, excess myostatin, and excess glucocorticoids. Numerous diseases can result in cachexia, each by a slightly different mechanism. Both nutritional support and orexigenic agents play a role in the management of cachexia. *Am J Clin Nutr* 2006;83:735–43.

KEY WORDS Cachexia, pathogenesis, sarcopenia, weight loss

INTRODUCTION

“...the shoulders, clavicles, chest and thighs melt away. This illness is fatal...”
—Hippocrates (460–370 BC)

Cachexia (*Gr. Kachexi 'a; kako's bad; 'e 'xis condition*) is a major cause of weight loss and increased mortality and affects more than 5 million people in the United States (**Table 1**) (1). Clinically, cachexia manifests with excessive weight loss in the setting of ongoing disease, usually with disproportionate muscle wasting (**Table 2**). Differentiation from other syndromes of weight loss is pivotal to prompt recognition and effective management of cachexia. Weight loss resulting from the syndrome of starvation occurs as a direct result of caloric deprivation. Starved persons generally lose more fat than muscle tissue. Sarcopenia is yet another weight-loss syndrome that results primarily from muscle atrophy due to a variety of causes. A fourth, often neglected, cause of weight loss is dehydration, in which fluid loss accounts for the reduction in measured weight (2, 3). Although numerous diseases are associated with cachexia, the underlying pathophysiologic mechanisms are unclear. This article reviews current pathogenetic theories related to common causes of cachexia.

CYTOKINES: A CENTRAL PLAYER IN THE PATHOGENESIS OF CACHEXIA

Cytokines are cell-associated proteins produced by inflammatory cells that function as paracrine intercellular mediators. Systemic inflammation mediated through cell injury or activation of

the immune system triggers an acute inflammatory response that causes excess cytokine elaboration. Cytokines play a major role in immunomodulation and have been implicated in the etiology of anorexia, weight loss, cognitive dysfunction, anemia, and frailty (4–8). Excessive elaboration of proinflammatory cytokines such as interleukin (IL) 1, IL-2, interferon γ , and tumor necrosis factor α (TNF- α) is probably the most common cause of cachexia observed in acutely ill patients (9) (**Figure 1**). Cytokines activate nuclear transcription factor κ B (NF- κ B), which results in decreased muscle protein synthesis (10, 11). Cytokine activation is also responsible for the reduction of MyoD protein, a transcription factor that modulates signaling pathways involved in muscle development (12). MyoD binding to myosin heavy chain IIb promoter region is necessary for myosin expression in fast twitch muscles (11). TNF- α and interferon γ act synergistically to inhibit the activation of messenger RNA for myosin heavy chain synthesis. TNF- α and interferon γ are highly specific for stimulating the proteolysis of myosin heavy chains (12).

Cytokines also activate the ubiquitin-mediated proteolytic system which, is the major system involved in disease-related hypercatabolism (13). Ubiquitin is a 76 amino acid, highly conserved polypeptide that targets specific proteins within skeletal muscle. Ubiquitinated proteins are delivered into the hollow core of the proteasome by attachment to the 19S component. Subsequent muscle proteolysis yields amino acids and oligopeptides that are consumed in hepatic synthesis of acute phase proteins such as C-reactive protein and serum amyloid peptide. The ubiquitin-proteasome system also indirectly modulates protein synthesis through degradation of inhibitory κ B protein (IKB)–NF κ B gene regulation. Additionally, cytokines stimulate the release of cortisol and catecholamines from the adrenal gland (14, 15). Cortisol further propagates the activity of the ubiquitin-proteasome system, and catecholamines lead to an increase in resting metabolic rate. Cytokines induce lipolysis and β -oxidation (16). Fat and liver lipoprotein lipase activity decrease, whereas LDL hepatocyte

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Received May 13, 2005.

Accepted for publication October 6, 2005.

TABLE 1
The number of persons in the United States with cachexia¹

Disease	No. with disease	Cachexia %	No. needing treatment
AIDS ²	900 000	35	315 000
Cancer	1 368 000	30	410 400
COPD	16 000 000	20	3 200 000
Kidney failure	375 000	40	150 000
Rheumatoid arthritis	2 100 000	10	210 000
Heart failure	4 800 000	20	960 000
Nursing home	1 600 000	20	320 000

¹ The numbers are based on generally reported prevalences of disease and literature estimations of unintentional weight loss in these conditions. COPD, chronic obstructive pulmonary disease.

² The values may be too high in the era of the use of highly active antiretroviral therapy; some authors believe that 10% may be more appropriate.

receptor activity increase (17, 18). Subsequent increased VLDL synthesis and decreased lipoprotein lipase activity hinder triacylglycerol clearance and result in hypertriglyceridemia (19). All these processes result in negative energy balance and weight loss (9). Notably, sickness behavior is also attributed to peripheral and central cytokine-mediated effects on the nervous system. Sickness behavior produces symptoms such as listlessness, malaise, and anhedonia, which further compromise energy intake. Abundant evidence highlighting the prominent role of cytokines in cachexia supports ongoing efforts to use cytokine antagonism as a therapeutic option in cachexia (**Table 3**).

OTHER POTENTIAL MEDIATORS OF THE CACHEXIA SYNDROME

Testosterone

Testosterone concentrations decline with aging and disease (20–22). Testosterone stimulates myoblasts and increases satellite cells, thereby promoting protein synthesis and efficient repair of damaged muscle (23). Testosterone also inhibits the macrophage release of proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6 (24, 25) and stimulates the production of IL-10, an antiinflammatory cytokine (26). Notably, low testosterone concentrations are associated with elevated circulating leptin concentrations. Leptin is an anorectic and lipolytic hormone produced by adipocytes (27). These changes probably account

TABLE 2
Diagnostic criteria for cachexia

Criteria
Unintentional weight loss ($\geq 5\%$)
BMI
<20 in those aged <65 y
<22 in those aged ≥ 65 y
Albumin < 35 g/L (3.5 g/dL)
Low fat-free mass (lowest 10%)
Evidence of cytokine excess (eg, elevated C-reactive protein)

for age- and disease-related anorexia, weight loss, and cachexia in some hypogonadal men (28–30).

Insulin-like growth factor I

Circulating Insulin-like growth factor I (IGF-I) concentrations are highly sensitive to food intake, increasing markedly during an overnight fast. However, limited evidence indicates that refeeding adequately restores IGF values to baseline. Short-term nutritional status, dietary micronutrient composition, and essential amino acid concentrations also seem to play an adjunctive role in determining IGF-I concentrations (31, 32).

IGF-I increases muscle protein synthesis. IGF-I concentrations increase with growth hormone and testosterone administration, thereby accounting for some of the effect of these hormones on muscle bulk and strength (33, 34). Stem cells that express the muscle isoform of IGF-I prevent sarcopenia in old rodents (35, 36). Low IGF-I concentrations in malnourished humans suggest a role for IGF-I in the pathogenesis of cachexia (37–39).

Myostatin

Myostatin is a hormone produced in muscle that suppresses muscle growth by inhibiting myoblast proliferation (40). Genetic myostatin deletions produce double-muscling cows and muscle hypertrophy in mice (41–43). Recently, a double myostatin deletion was identified in a 1-y-old child with extreme muscle hypertrophy (44). Transgenic mice with the myostatin gene develop a cachexia-like syndrome that manifests with severe wasting (45). Similar human models have not been identified. Additionally, myostatin assays in humans have technical limitations.

Adrenal hormones

Glucocorticoids suppress glucose and amino acid muscle uptake by inhibiting cellular transporters (46, 47). Glucocorticoids have a permissive effect on the up-regulation of messenger RNA and the subsequent synthesis of components of the ubiquitin-proteasome system in muscle (13, 48). Glucocorticoids also inhibit protein synthesis and promote gluconeogenesis, which contributes to steroid-induced myopathy and impaired glucose tolerance. Elevated glucocorticoids in cachectic patients may contribute to ongoing proteolysis and impaired protein synthesis.

DISEASE AND CACHEXIA

Cardiac cachexia

The excessive elaboration of pro-inflammatory cytokines have been implicated in cardiac cachexia (49–52). In the Framingham Study, elderly subjects with no history of myocardial infarction or congestive heart failure had a significant increase in congestive heart failure risk per tertile increment in cytokine concentration (60% for TNF- α and 68% for serum IL-6). Data also show that the highest concentrations of TNF- α are associated with the poorest functional status in patients with congestive heart failure (53) (**Figure 2**).

Reversal of weight loss predicts improved outcomes in patients with cardiac cachexia undergoing treatment (54). Angiotensin-converting-enzyme inhibitors reduce circulating

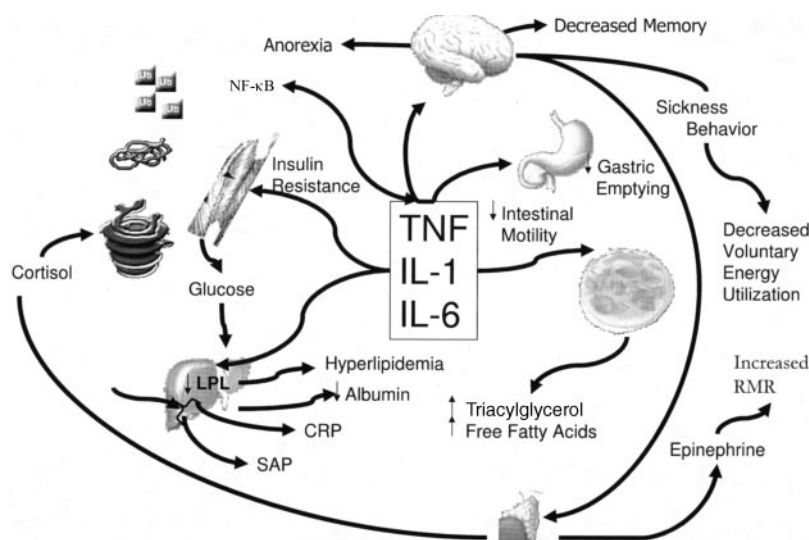


FIGURE 1. The pathophysiologic role of cytokines in the production of cachexia. TNF, tumor necrosis factor; IL-1, interleukin 1; IL-6, interleukin 6; RMR, resting metabolic rate; LPL, lipoprotein lipase; CRP, C-reactive protein; SAP, serum amyloid protein.

concentrations of IL-1 (55), TNF- α (56), and IL-6 (57) and reduce the risk of weight loss (50). However, studies of entanercept, a TNF-receptor blocker (58, 59), and TNF antibodies (60) in patients with congestive failure did not improve outcomes.

Chronic renal failure

More than 25% of patients receiving hemodialysis are malnourished (61, 62). Two types of malnutrition occur in chronic renal failure: starvation and cachexia (**Table 4**). Starvation is predominantly due to poor energy intake and is characterized by a lack of inflammation and normal albumin concentrations (63). Adequate dialysis and nutritional support improve appetite and nutritional status in starved patients. In contrast, cachexia is associated with systemic inflammation, enhanced proteolysis, and excessive oxidative stress. Affected patients have elevated serum C-reactive protein concentrations, high cytokine concentrations, and hypoalbuminemia. Available data indicate that optimal outcomes in the treatment of cachectic patients are achieved by combined therapy with dialysis, anticytokine therapy, erythropoietin supplementation, and nutritional support. This multipronged approach has been shown to prolong survival, increase energy tolerance, and increase body weight (64, 65).

Pathogenetic theories of malnutrition in renal failure implicate both hypercatabolism and anorexia (63, 66). Anorexia of renal failure is due to several factors: cytokine excess, gastroparesis, glucose absorption from the dialysate, medication, increased leptin concentrations, and zinc deficiency (67, 68). Hypercatabolism in renal failure is attributed to cytokine excess, inadequate dialysis, acidosis, infections, and insulin resistance (69).

Chronic obstructive pulmonary disease

Weight loss in patients with chronic obstructive pulmonary disease (COPD) is associated with muscle weakness, diaphragmatic dysfunction (70), respiratory failure, and poor quality of life and death (71, 72). Factors that contribute to weight loss in COPD include hypercatabolism, medications, anorexia, and the effect of increased thermic effect of eating on total energy expenditure (TEE) (73). Clinically stable patients with COPD and

weight loss have significantly higher serum TNF- α concentrations than do their counterparts with similar degrees of disease (74). At the molecular level, up-regulation of NF- κ B and inducible nitric oxide synthase (iNOS) occur in the skeletal muscle of patients with COPD and cachexia, which results in impaired protein synthesis (75).

Oral energy supplementation has no effect on anthropomorphic measures, lung function, or exercise tolerance in patients with COPD (76). Studies that examined the efficacy of cytokine antagonism, using megestrol acetate, in patients with COPD and cachexia showed improved appetite, weight gain, and increased exercise tolerance (77). Although testosterone concentrations are low in patients with COPD (78), replacement therapy failed to improve exercise tolerance despite an increase in body weight (79).

Anorexia-cachexia syndrome in cancer

Weight loss is a complaint of 15–40% of cancer patients and indicates poor prognosis. Cytokine induction in cancer has been well described. Peripheral and central mechanisms have been implicated (**Figure 3, A and B**). Cytokine production in malignant disease increases corticotrophin releasing factor, a potent anorectic agent, and, in concert with prostaglandins, suppresses

TABLE 3

Drugs that act as cytokine antagonists

Cytokine antagonists

Progestagens
Thalidomide
Testosterone
Pentoxiphylline
NSAIDs ¹
Eicosapentaenoic acid
Cytokine antibodies
Soluble cytokine receptors
Angiotensin-converting-enzyme inhibitors
Statins

¹ Nonsteroidal antiinflammatory drugs.

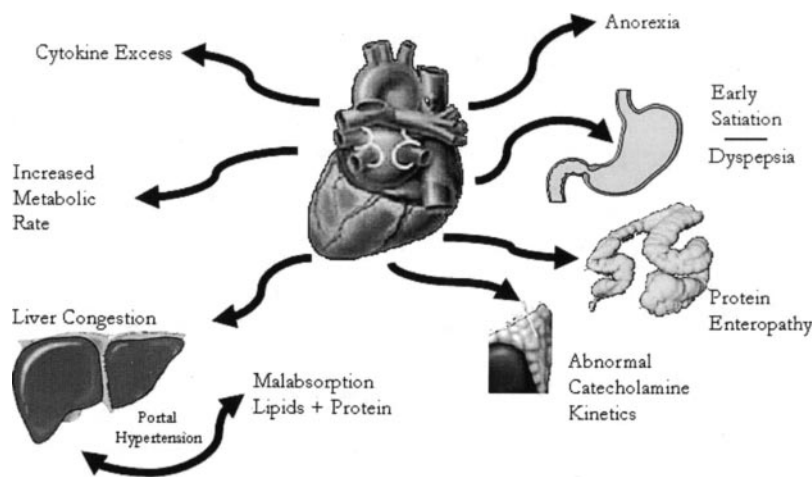


FIGURE 2. The pathophysiology of cardiac cachexia.

the production of the orexigenic agent neuropeptide Y (80, 81). Proteolysis is stimulated within muscle by activation of the proteasome system and transcription factor NF- κ B. Cytokines also delay gastric emptying, lower serum albumin concentrations, and enhance lipolysis (82, 83). Lipid mobilizing factor, a zinc α_2 -glycoprotein, activates cyclic adenosine-5-monophosphate in adipocytes, which results in the release of free fatty acids and glycerol into the circulation (84). Excessive lactate production from tumor cells exacerbates energy wasting by inducing the Cori Cycle in the liver and extrahepatic tissues (80).

Nutritional support enhances quality of life but does not improve mortality rates associated with most cancers (85, 86). Excessive proteolysis in cancer-anorexia syndrome can be abated with anabolic hormones, β_2 adrenergic agents, or cytokine inhibitors (87). Appetite stimulants such as dronabinol, an endogenous cannabinoid receptor agonist, and megestrol acetate (a cytokine antagonist) may be helpful. Data indicate that megestrol acetate is more effective than is dronabinol (88). Conflicting evidence exists regarding the efficacy of androgenic steroids.

Eicosopentaenoic acid decreases proinflammatory cytokines (89) and suppresses ubiquitin-proteasome-induced muscle proteolysis (90). Eicosopentaenoic acid stabilized weight in some trials of patients with advanced cancer (91). Recent studies have also shown significant increases in weight gain, lean body mass, and quality of life after treatment of cachexia with eicosopentaenoic acid (92).

A pilot study that examined the effect of infliximab, an immunoglobulin G antibody that blocks TNF- α receptors, showed weight stability in 1 of 4 patients with metastatic small cell lung cancer (93). Cori Cycle inhibitors, such as hydrazine, are not helpful (80).

Rheumatoid arthritis and cachexia

Sixty-seven percent of subjects with rheumatoid arthritis (RA) in the United States are cachectic. Studies indicate that, although body weight (94) and body mass index (95) are normal in most patients with RA, body cell mass is reduced. Loss of body cell mass is independent of duration of disease, therapy, or energy intake. Resting energy expenditure (REE) is also higher in cases than in control subjects. Furthermore, energy expended at rest and during activity increases with the severity of RA (94, 96). However, TEE is lower in patients with RA than in control

subjects (97). Because reduced physical activity is the main determinant of lower TEE in patients with RA, the net effect of an increase in REE and TEE coupled with unchanged energy intake results in a progressive loss of body cell mass. In studies of RA, approximately one-third of mobilizable body cell mass has been lost despite clinically well-controlled RA. Data from subjects with cancer, AIDS, and critical illness suggest that a loss of $\approx 40\%$ of body cell mass is fatal (98).

RA is also associated with cytokine excess. Synovial fluid and sera of affected patients contains high concentrations of TNF- α and IL-1 β (99, 100). Elevated production of TNF- α and IL-1 β has been described in RA during periods of disease activity. However, cytokine concentrations are undetectable during the quiescent phases of disease (101).

AIDS-related cachexia (wasting syndrome)

Cachexia associated with AIDS is highly predictive of death (102, 103). Common causes of AIDS wasting include anorexia, depression, medications, coexisting infections, and a variety of gastrointestinal diseases (Figure 4) (73, 104), eg, microsporidia, cryptosporidium, *Giardia lamblia*, cytomegalovirus, and *Mycobacterium avium*. Hypogonadism occurs commonly in males with AIDS (105), and elevated myostatin concentrations have been reported in AIDS patients (106). Overall, elaboration of proinflammatory cytokines is probably the major factor responsible for AIDS wasting.

Anabolic steroids have been reported to increase muscle mass and strength in patients with AIDS, although resistance exercise is just as effective (107, 108). Growth hormone increases muscle

TABLE 4
Types of malnutrition in chronic renal failure¹

Type 1: starvation	Type 2: cachexia
Normal or low serum albumin	Low serum albumin
Absence of inflammation (normal CRP)	Inflammation (elevated CRP)
Decreased protein catabolism	Increased protein catabolism
Low food intake	Low or normal food intake
Normal resting energy metabolism	Elevated resting energy metabolism
Small increase in oxidative stress	Markedly increased oxidation stress
Reversed by adequate dialysis and nutritional support	Resistant to increased dialysis and nutrition support

¹ CRP, C-reactive protein.

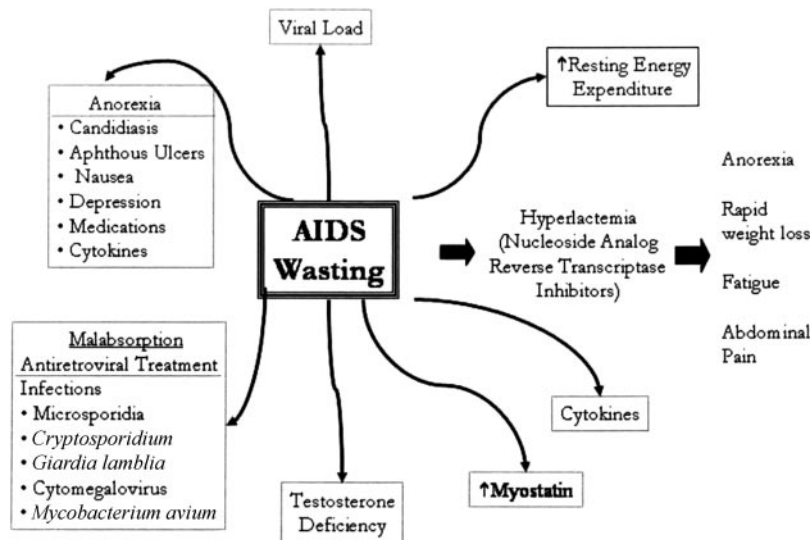


FIGURE 4. The pathophysiology of AIDS wasting.


such as Alzheimer disease, Parkinson disease, atherosclerosis, sarcopenia, and osteoporosis. It is not clear whether changes in cytokine concentrations are due to age itself or to underlying disease. Elevated plasma concentrations of IL-6 with aging may arise as a result of catecholamine hypersecretion and sex-steroid hyposcretion (118). Overall, the data suggest that low-grade inflammatory activity in older subjects is caused by dysregulated cytokine production, which is further exacerbated by age-associated pathology (119–123).

Weight loss with aging may also be attributed to a physiologic reduction in energy intake with aging, age-related gastric dysmotility, and impaired fundal compliance. This results in a failure of adaptive gastric relaxation and early satiation due to rapid passage of food into the atrium. Other factors include an age-related increase in the satiating effect of cholecystokinin and increased concentrations of amylin in older adults. Anorexia may be a consequence of hyperleptinemia in hypogonadal men and postmenopausal women (124). Rodent studies suggest that an age-related reduction in central nitric oxide synthase concentrations may be a pivotal factor (125) in modulating food intake (126, 127).

Physiologic anorexia of aging puts older persons at increased risk of developing cachexia, even during minor illnesses (128, 129). Additional factors, such as dysgeusia, dysnomia, orogingival disease, chronic pain, social isolation, and depression exacerbate the risk of weight loss (130–133).

Oral caloric supplementation between meals reduces length of hospital stay and mortality in the elderly (134, 135). Clear benefits of tube feeding in nutritional repletion have not been established. Indeed, evidence exists that tube feeding does not improve outcomes in dementia (136–140). In placebo controlled trials, monotherapy with either megestrol acetate or testosterone has been shown to increase weight (141). Weight gain with megestrol acetate was more prominent in persons with elevated cytokine concentrations (142). Overall, limited information exists to determine the appropriate use of orexigenics in older persons with cachexia (143).

CONCLUSION

Cachexia is a common problem in persons with severe disease and is highly predictive of increased mortality. Cachexia also contributes to the decline in quality of life that accompanies end-stage disease. Clearly, the etiology of cachexia is multifactorial. Nonetheless, emerging evidence suggests that cytokines play a central role in the pathogenesis of cachexia. Nutritional support alone may be inadequate in the management of cachexia. There is an emerging role for orexigenic agents in the management of cachexia, although further well-controlled studies are necessary to determine their appropriate use. 

JEM, DRT, and M-MGW were responsible for manuscript preparation, drafting, and consultation. All authors contributed evenly to the construction of this review. JEM received consulting fees from Merck Manuals, Mattern Pharmaceuticals, and PAR Pharmaceuticals. DRT received consulting fees from Forest Pharmaceuticals. M-MGW received lecture fees from PAR Pharmaceuticals.

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