

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

John E Morley, David R Thomas, and Margaret-Mary G Wilson

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 IIIb 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

¹ From the Division of Geriatric Medicine, Saint Louis University School of Medicine, St Louis, MO (JEM, DRT, and M-MGW), and GRECC, VA Medical Center, Saint Louis, MO (JEM).

² Reprints not available. Address correspondence to JE Morley, Division of Geriatric Medicine, Saint Louis University School of Medicine, 1402 South Grand Boulevard, M238, St Louis, MO 63104. E-mail: morley@slu.edu.

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

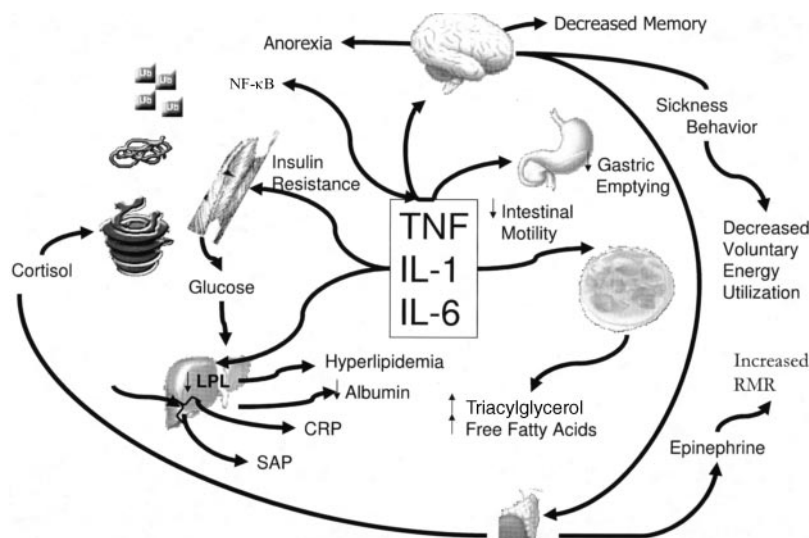


FIGURE 1. The pathophysiologic role of cytokines in the production of cachexia. TNF, tumor necrosis factor; IL-1, interleukin 1; IL-6, interleukin 6; RMR, resting metabolic rate; LPL, lipoprotein lipase; CRP, C-reactive protein; SAP, serum amyloid protein.

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.

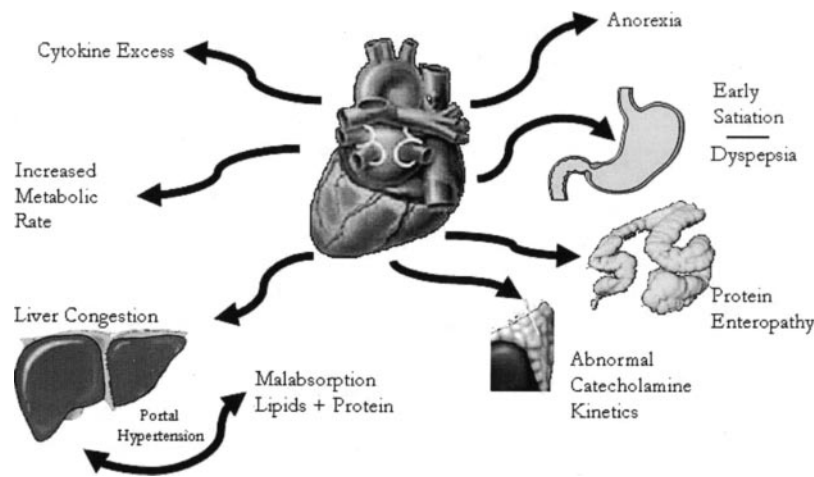


FIGURE 2. The pathophysiology of cardiac cachexia.

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.

Eicosapentaenoic acid decreases proinflammatory cytokines (89) and suppresses ubiquitin-proteasome-induced muscle proteolysis (90). Eicosapentaenoic 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 eicosapentaenoic 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.

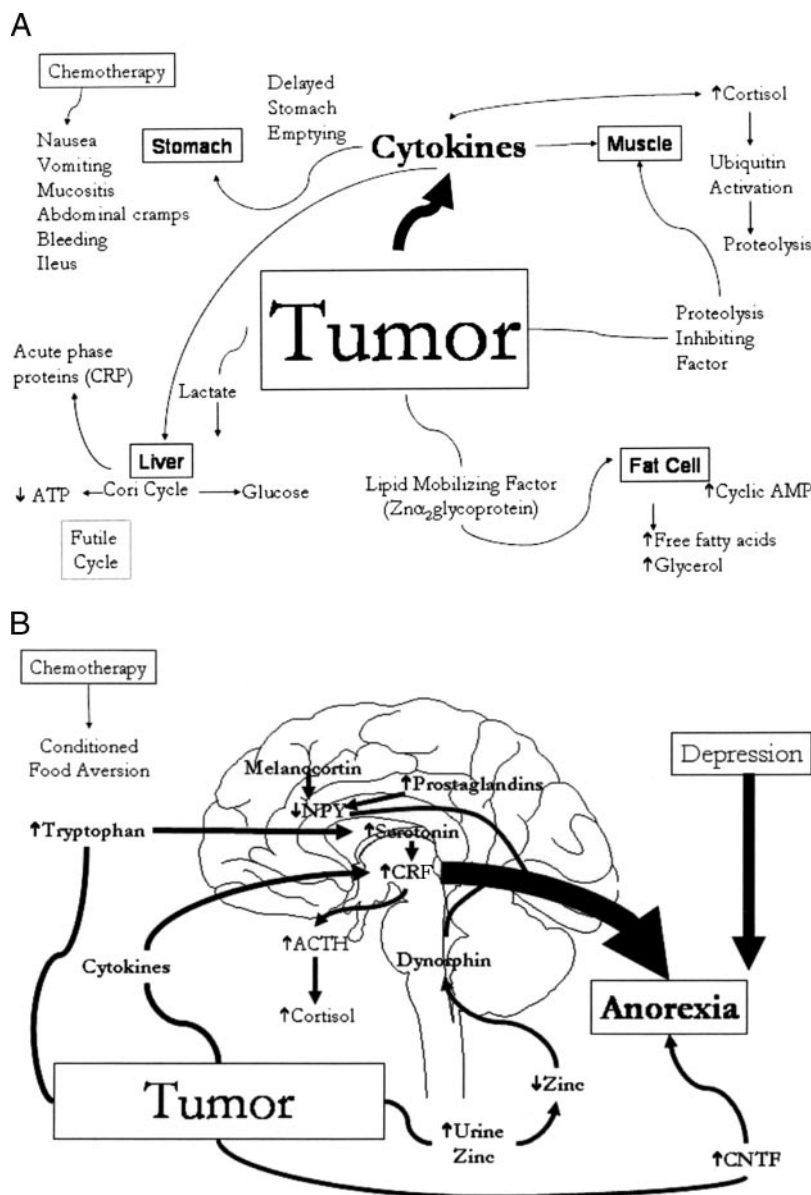


FIGURE 3. The peripheral (A) and central (B) mechanisms producing anorexia-cachexia syndrome in cancer. CRP, C-reactive protein; NPY, neuropeptide Y; CRF, chronic renal failure; ACTH, adrenocorticotrophic hormone; CNTF, ciliary neurotrophic factor.

mass, physical function, body weight, and quality of life in patients with AIDS (109, 110). However, patients with markedly elevated concentrations of TNF- α receptor 2 are resistant to the anabolic effect of growth hormone on muscle (111). Megestrol acetate has been shown to increase appetite, weight, and quality of life in patients with AIDS-related cachexia (112, 113). A direct comparison between oxandralone and megestrol acetate showed that both produced similar increases in weight and lean body mass (114). Monotherapy with dronabinol was associated with weight loss. Direct comparison of dronabinol alone, megestrol alone, and both drugs given in combination showed weight gain with megestrol alone and with combined therapy. However, weight gain was somewhat less when both drugs were used in combination (113). AIDS-related cachexia remains a major problem. Further randomized controlled studies are needed to

objectively define the efficacy of testosterone, growth hormone, and cytokine antagonists in this condition.

Aging and weight loss

Weight loss in older adults is highly predictive of increased morbidity and mortality (115–117). Several factors contribute to weight loss in older adults. Available data indicate that excess cytokine elaboration may be a critical factor in the induction of involuntary weight loss in older adults. Aging is associated with increased concentrations of TNF- α , IL-6, IL1 receptor antagonist, and soluble TNF receptor. Acute phase proteins such as C-reactive protein and serum amyloid A are also elevated, which suggests the activation of the entire inflammatory cascade. Proinflammatory cytokines are also thought to play a pathogenetic role in other age-related diseases,

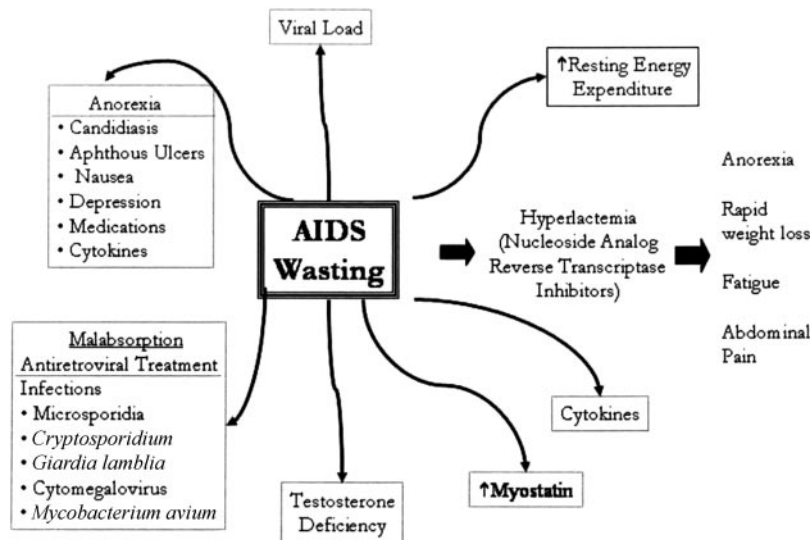


FIGURE 4. The pathophysiology of AIDS wasting.


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 hyposalivation (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.

REFERENCES

- Sharma R, Anker S. First cachexia symposium. Berlin, Germany: 1st-2nd December, 2000. *Eur J Heart Fail* 2000;3:751–4.
- Thomas DR. Distinguishing starvation from cachexia. *Clin Geriatr Med* 2002;18:883–91.
- Roubenoff R, Heymsfield SB, Kehayias JJ, Cannon JG, Rosenberg IH. Standardization of nomenclature of body composition in weight loss. *Am J Clin Nutr* 1997;66:192–6.
- Roubenoff R, Parise H, Payette HA, et al. Cytokines, insulin-like growth factor 1, sarcopenia, and mortality in very old community-dwelling men and women: the Framingham Heart Study. *Am J Med* 2003;115:429–35.
- Ferrucci L, Penninx BWJH, Volpato S, et al. Change in muscle strength explains accelerated decline in physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc* 2002;50:1947–54.
- Morley JE. Anorexia, sarcopenia, and aging. *Nutrition* 2001;17:660–3.
- Morley JE, Baumgartner R. Cytokine related aging process. *J Gerontol Med Sci* 2004;59A:924–9.
- Wilkinson TJ, Warren MR. What is the prognosis of mild normocytic anemia in older people? *Int Med J* 2003;33:14–7.
- Kotler DP. Cachexia. *Ann Intern Med* 2000;133:622–34.
- Guttridge DC, Mayo MW, Madrid LV, Wang CY, Baldwin AS Jr.



- NF- κ B-induced loss of MyoD messenger RNA; possible role in muscle decay and cachexia. *Science* 2000;289:2363–6.
11. Wheeler MT, Snyder EC, Patterson MN, Swoap SJ. An E-box within the MHC IIB gene is bound by MyoD and is required for gene expression in fast muscle. *Am J Physiol* 1999;276:C1069–78.
 12. Acharyya S, Ladner KJ, Nelsen LL, et al. Cancer cachexia is regulated by selective targeting of skeletal muscle gene products. *Cancer cachexia is regulated by selective targeting of skeletal muscle gene products*. *J Clin Invest* 2004;114:370–8.
 13. Mitch WE, Goldberg AL. Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. *N Engl J Med* 1996;335:1897–905.
 14. Shintani F, Nakaki T, Kanba S, Kato R, Asai M. Role of interleukin-1 in stress responses. A putative neurotransmitter. *Mol Neurobiol* 1995;10:47–71.
 15. Pende A, Musso NR, Vergassola C, et al. Neuroendocrine effects of interferon alpha 2-a in healthy human subjects. *J Biol Regul Homeost Agents* 1990;4:67–72.
 16. Ryden M, Arvidsson E, Blomqvist L, Perbeck L, Dicker A, Arner P. Targets for TNF-alpha-induced lipolysis in human adipocytes. *Biochem Biophys Res Commun* 2004;318:168–75.
 17. Liao W, Floren CH. Upregulation of low density lipoprotein receptor activity by tumor necrosis factor, a process independent of tumor necrosis factor-induced lipid synthesis and secretion. *Lipids* 1994;29:679–84.
 18. Feingold KR, Marshall M, Gulli R, Moser AH, Grunfeld C. Effect of endotoxin and cytokines on lipoprotein lipase activity in mice. *Arterioscler Thromb* 1994;14:1866–72.
 19. Grunfeld C, Feingold KR. Regulation of lipid metabolism by cytokines during host defense. *Nutrition* 1996;12(suppl):S24–6.
 20. Morley JE, Kaiser FE, Perry HM, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metab Clin Exp* 1997;46:410–3.
 21. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab* 2001;86:724–31.
 22. Morley JE, Melmed S. Gonadal dysfunction in systemic disorders. *Metabolism* 1979;28:1051–73.
 23. Bhasin S, Taylor WE, Singh R, et al. The mechanisms of androgen effects on body composition: mesenchymal pluripotent cell as the target of androgen action. *J Gerontol Med Sci* 2003;58A:M1103–10.
 24. D'Agostino P, Milano S, Barbera C, et al. Sex hormone modulate inflammatory mediators produced by macrophages. *Ann N Y Acad Sci* 1999;876:426–9.
 25. Li ZG, Danis VA, Brooks PM. Effect of gonadal steroids on the production of IL-1 and IL-6 by blood mononuclear cells in vitro. *Clin Exp Rheumatol* 1993;11:157–62.
 26. Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. *J Clin Endocrinol Metab* 2004;89:3313–8.
 27. Baumgartner RN, Waters DL, Morley JE, Patrick P, Montoya GD, Garry PJ. Age-related changes in sex hormones affect the sex difference in serum leptin independently of changes in body fat. *Metab Clin Exp* 1999;48:378–84.
 28. Sih R, Morley JE, Kaiser Fe, Perry HM, Patrick P, Ross C. Testosterone replacement in older hypogonadal men—a 12-month randomized controlled trial. *J Clin Endocrinol Metab* 1997;82:1661–7.
 29. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. *Mech Ageing Dev* 1999;107:123–36.
 30. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. *J Gerontol Med Sci* 2002;57A:M772–7.
 31. Giovannucci E, Pollak M, Liu Y, et al. Nutritional predictors of insulin-like growth factor I and their relationships to cancer in men. *Cancer Epidemiol Biomarkers Prev* 2003;12:84–9.
 32. Allen NE, Appleby PN, Davey GK, Kaaks R, Rinaldi S, Key TJ. The associations of diet with serum insulin-like growth factor I and its main binding proteins in 292 women meat-eaters, vegetarians, and vegans. *Cancer Epidemiol Biomarkers Prev* 2002;11:1441–8.
 33. Fang CH, Li BG, Wang JJ, Fischer JE, Hasselgren PO. Insulin-like growth factor I stimulates protein synthesis and inhibits protein breakdown in muscle from burned rats. *J Parenter Enteral Nutr* 1997;21:245–51.
 34. Tirapegui J. Effect of insulin-like growth factor-1 (IGF-1) on muscle and bone growth in experimental models. *Int J Food Sci Nutr* 1999;50:231–6.
 35. Barton ER, Morris L, Musaro A, Rosenthal N, Sweeney HL. Muscle-specific expression of insulin-like growth factor I counters muscle decline in MDX mice. *J Cell Biol* 2002;157:137–47.
 36. Musaro A, McCullagh K, Paul A, et al. Localized IGF-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. *Nat Genet* 2001;27:195–200.
 37. Caregaro L, Favaro A, Santonastaso P, et al. Insulin-like growth factor 1 (IGF-1), a nutritional marker in patients with eating disorders. *Clin Nutr* 2001;20:251–7.
 38. Ponzer S, Tidermark J, Brismar K, Soderqvist A, Cederholm T. Nutritional status, insulin-like growth factor-1 and quality of life in elderly women with hip fractures. *Clin Nutr* 1999;18:241–6.
 39. Caregaro L, Alberino F, Amodio P, et al. Nutritional and prognostic significance of insulin-like growth factor 1 in patients with liver cirrhosis. *Nutrition* 1997;13:185–90.
 40. Roth SM, Walsh S. Myostatin: a therapeutic target for skeletal muscle wasting. *Curr Opin Clin Nutr Metab Care* 2004;7:259–63.
 41. McPherron AC, Lee S-J. Double muscling in cattle due to mutations in the myostatin gene. *Proc Natl Acad Sci U S A* 1997;94:12457–61.
 42. Grobet L, Martin LJR, Poncelet D, et al. A deletion in the bovine myostatin gene causes the double-muscling phenotype in cattle. *Nat Genet* 1997;17:71–4.
 43. Lin J, Arnold HB, Della-Fera MA, et al. Myostatin knockout in mice increases myogenesis and decreases adipogenesis. *Biochem Biophys Res Commun* 2002;291:701–6.
 44. Schuelke M, Wagner KR, Stolz LE, et al. Brief report—myostatin mutation associated with gross muscle hypertrophy in a child. *N Engl J Med* 2004;250:2682–8.
 45. Zimmers TA, Davies MV, Koniaris LG, et al. Induction of cachexia in mice by systemically administered myostatin. *Science* 2002;296:1486–8.
 46. Ewart HS, Somwar R, Klip A. Dexamethasone stimulates the expression of GLUT1 and GLUT4 proteins with different signaling pathways in L6 skeletal muscle cells. *FEBS Lett* 1998;425:179–83.
 47. Dimitriadis G, Leighton B, Parry-Billings M, et al. Effects of glucocorticoid excess on the sensitivity of glucose transport and metabolism to insulin in rat skeletal muscle. *Biochem J* 1997;321:707–12.
 48. Wing SS, Goldberg AL. Glucocorticoids activate the ATP-ubiquitin-dependent proteolytic system in skeletal muscle during fasting. *Am J Physiol* 1993;264:E668–76.
 49. Anker SD, Negassa A, Coats AJ, et al. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003;361:1077–83.
 50. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302.
 51. Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart* 2004;90:464–70.
 52. Anker SD, Ponikowski PP, Clark AL, et al. Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure. *Eur Heart J* 1999;20:683–93.
 53. Ciccoira M, Bolger AP, Doehner W, et al. High tumour necrosis factor-alpha levels are associated with exercise intolerance and neurohormonal activation in chronic heart failure patients. *Cytokine* 2001;15:80–6.
 54. Anker SD. Has the time arrived to use anticytokine therapy in chronic heart failure. *Dialogues Cardiovasc Med* 2000;5:162–70.
 55. Liu L, Zhao SP. The changes of circulating tumor necrosis factor levels in patients with congestive heart failure influenced by therapy. *Int J Cardiol* 1999;69:77–82.
 56. Gullestad L, Aukrust P, Ueland T, et al. Effect of high-versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. *J Am Coll Cardiol* 1999;34:2061–7.
 57. Sigurdsson A, Swedberg K, Ullman B. Effects of ramipril on the neurohormonal response to exercise in patients with mild or moderate congestive heart failure. *Eur Heart J* 1994;15:247–54.
 58. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy



- in patients with chronic heart failure: results of Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004; 109:1594–602.
59. Bozkurt B, Torre-Amione G, Warren MS, et al. Results of targeted anti-tumor necrosis factor therapy with etanercept in patients with advanced heart failure. *Circulation* 2001;103:1044–7.
 60. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT, AntiTNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACHF) trial. *Circulation* 2003; 107:3133–40.
 61. Cano W. Malnutrition and chronic renal failure. *Ann Med Interne (Paris)* 2000;151:563–74.
 62. Garg AX, Blake PG, Clark WF, Clase CM, Haynes RB, Moist LM. Association between renal insufficiency and malnutrition in older adults: results from the NHAMES III. *Kidney Int* 2001;60:1867–74.
 63. Guarnieri G, Toigo G, Fiotti N, et al. Mechanisms of malnutrition in uremia. *Kidney Int* 1997;62(suppl):S41–4.
 64. Kalantar-Zadeh K, Stenvinkel P, Bross R, et al. Kidney insufficiency and nutrient-based modulation of inflammation. *Curr Opin Clin Nutr Metab Care* 2005;8:388–96.
 65. Lundholm K, Daneryd P, Bosaeus I, Korner U, Lindholm E. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: effects on survival, metabolism, and function. *Cancer* 2004;100:1967–77.
 66. Bergstrom J. Regulation of appetite in chronic renal failure. *Miner Electrolyte Metab* 1999;25:291–7.
 67. Van Vlem B, Schoonjans R, Vanholder R, et al. Delayed gastric emptying in dyspeptic chronic hemodialysis patients. *Am J Kidney Dis* 2000;36:962–8.
 68. De Schoenmakere G, Vanholder R, Rottey S, Duym P, Lameire N. Relationship between gastric emptying and clinical and biochemical factors in chronic hemodialysis patients. *Nephrol Dial Transplant* 2001;16:1850–5.
 69. Mitch WE, Du J, Bailey JL, Price SR. Mechanisms causing muscle proteolysis in uremia: the influence of insulin and cytokines. *Miner Electrolyte Metab* 1999;25:216–9.
 70. Reid MB. COPD as a muscle disease. *Am J Respir Crit Care Med* 2001;164:1101–2.
 71. Schols AM, Slangen J, Volovics L, et al. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;157:1791–7.
 72. Mostert R, Goris A, Weling-Scheepers C, et al. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. *Respir Med* 2000;94:859–67.
 73. Farber MO, Mannix ET. Tissue wasting in patients with chronic obstructive pulmonary disease, the acquired immune deficiency syndrome, and congestive heart failure. *Neurol Clin* 2000;18:245–62.
 74. Hasegawa Y, Sawada M, Ozaki N, et al. Increased soluble tumor necrosis factor receptor levels in the serum of elderly people. *Gerontology* 2000;46:185–8.
 75. Agusti A, Morla M, Sauleda J, Saus C, Busquets X. NF-kappa β activation and iNOS upregulation in skeletal muscle of patients with COPD and low body weight. *Thorax* 2004;59:483–7.
 76. Schols A. Nutritional modulation as part of the integrated management of chronic obstructive pulmonary disease. *Proc Nutr Soc* 2003;62:783–91.
 77. Weisberg J, Wanger J, Olson J, et al. Megestrol acetate stimulates weight gain and ventilation in underweight COPD patients. *Chest* 2002; 121:1070–8.
 78. Kimischke A, Kemper DE, Castel MA, et al. Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. *Eur Respir J* 1998;11:41–5.
 79. Yeh SS, DeGuzman B, Kramer T. Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. *Chest* 2002;122: 421–8.
 80. Inui A. Cancer anorexia-cachexia syndrome: current issues in research management. *CA Cancer J Clin* 2002;52:72–91.
 81. Behan DP, Grigoriadis DE, Lovenberg T, et al. Neurobiology of corticotrophin releasing factor (CRF) receptors and CRF-binding protein: implications for the treatment of CNS disorders. *Mol Psychiatry* 1996; 1:265–77.
 82. Ramos EJ, Suzuki S, Marks D, Inui A, Asakawa A, Meguid MM. Cancer anorexia-cachexia syndrome: cytokines and neuropeptides. *Curr Opin Clin Nutr Metab Care* 2004;7:427–34.
 83. Davis MP, Dreicer R, Walsh D, Lagman R, LeGrand SB. Appetite and cancer-associated anorexia: a review. *J Clin Oncol* 2004;22:1510–7.
 84. Russell ST, Zimmerman TP, Domin BA, Tisdale MJ. Induction of lipolysis in vitro and loss of body fat in vivo by zinc alpha2-glycoprotein. *Biochim Biophys Acta* 2004;1636:59–68.
 85. Jatoi A, Rowland K, Loprinzi CL, et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute Canada collaborative effort. *J Clin Oncol* 2004;22:2469–76.
 86. Grobbelaar EJ, Owen S, Torrance AD, Wilson JA. Nutritional challenges in head and neck cancer. *Clin Otolaryngol Allied Sci* 2004;29: 307–13.
 87. Argiles JM, Almendro V, Busquets S, Lopez-Soriano FJ. The pharmacological treatment of cachexia. *Curr Drug Targets* 2004;5:265–77.
 88. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002;20: 2912–3.
 89. Jho D, Babcock TA, Helton WS, Espat NJ. Omega-3 fatty acids: implications for the treatment of tumor-associated inflammation. *Am Surg* 2003;69:32–6.
 90. Tisdale MJ. The 'cancer cachectic factor.' *Support Care Cancer* 2003; 11:73–78.
 91. Bruera E, Strasser F, Palmer JL, et al. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: a double-blind, placebo-controlled study. *J Clin Oncol* 2003;21: 129–34.
 92. Fearon KC, von Meyenfeldt MF, Moses AAG, et al. Effect of a protein and energy dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomized double blind trial. *Gut* 2003;52:1479–86.
 93. Jatoi A, Jett JR, Sloan J, et al. A pilot study on safety and pharmacokinetics of infliximab for the cancer anorexia/weight loss syndrome in non-small-cell lung cancer patients. *Support Care Cancer* 2004;12: 859–63.
 94. Roubenoff R, Roubenoff RA, Cannon JG, et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. *J Clin Invest* 1994;93:2379–86.
 95. Walsmith J, Abad L, Kehayias J, Roubenoff R. Tumor necrosis factor-alpha production is associated with less body cell mass in women with rheumatoid arthritis. *J Rheumatol* 2004;31:23–9.
 96. De Carvalho MRP, Tebexreni AS, Salles CAF, Neto TLB, Natour J. Oxygen uptake during walking in patients with rheumatoid arthritis—a controlled study. *J Rheumatol* 2004;31:655–62.
 97. Roubenoff R, Walsmith J, Lundgren N, Snyderman L, Dolnikowski GJ, Roberts S. Low physical activity reduces total energy expenditure in women with rheumatoid arthritis: implications for dietary intake recommendations. *Am J Clin Nutr* 2002;76:774–9.
 98. Grunfeld C, Feingold KR. Metabolic disturbances and wasting in the acquired immunodeficiency syndrome. *N Engl J Med* 1992;327:329–37.
 99. Eastgate JA, Wood NC, DiGiovine FS, Symons JA, Grinlinton FM, Duff GW. Correlation of plasma interleukin-1 levels with disease activity in rheumatoid arthritis. *Lancet* 1988;2:706–9.
 100. Saxne T, Palladino MA, Heinegard D, Talal N, Wollheim FA. Detection of tumor necrosis factor-alpha but not tumor necrosis factor-beta in rheumatoid arthritis synovial fluid and serum. *Arthritis Rheum* 1988; 31:1041–4.
 101. Roubenoff R, Roubenoff RA, Ward LM, Stevens MB. Catabolic effects of high-dose corticosteroids persist despite therapeutic benefit in rheumatoid arthritis. *Am J Clin Nutr* 1990;52:1113–7.
 102. Grinspoon S, Mulligan K. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis* 2003;236(suppl): S69–78.
 103. Rodolphe T, Denis M, Catherine M, Francois D. Anthropometric indices as predictors of survival in AIDS adults. Aquitaine Cohort, France, 1985–1997. *Eur J Epidemiol* 2000;16:633–9.
 104. Dolan S, Wilkie S, Aliabadi N, et al. Effects of testosterone administration in human immunodeficiency virus-infected women with low



- weight—a randomized placebo-controlled study. *Arch Intern Med* 2004;164:897–904.
105. Rietschel P, Corcoran C, Stanley T, Basgoz N, Klibanski A, Grinspoon S. Prevalence of hypogonadism among men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy. *Clin Infect Dis* 2000;31:1240–4.
 106. Gonzalez-Cadavid NF, Taylor WE, Yarasheski K, et al. Organization of the human myostatin gene and expression in healthy men and HIV-infected men with muscle wasting. *Proc Natl Acad Sci U S A* 1998;95:14938–43.
 107. Grinspoon S, Corcoran C, Parلمان K, et al. Effects of testosterone and progressive resistance training in eugonadal men with AIDS wasting—a randomized, controlled trial. *Ann Intern Med* 2000;133:348–55.
 108. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA* 2000;283:763–70.
 109. Cominelli S, Raguso CA, Karsegard L, et al. Weight-losing HIV-infected patients on recombinant human growth hormone for 12 weeks: a national study. *Nutrition* 2002;18:583–6.
 110. Moyle GJ, Daar ES, Gertner JM, et al. Growth hormone improves lean body mass, physical performance, and quality of life in subjects with HIV-associated weight loss or wasting on highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2004;35:367–75.
 111. Gelato MC, Mynarcik D, McNurlan MA. Soluble tumour necrosis factor alpha receptor 2, a serum marker of resistance of the anabolic actions of growth hormone in subjects with HIV disease. *Clin Sci* 2002;102:85–90.
 112. Von Roenn JH, Armstrong D, Kotler DP, et al. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med* 1994;121:393–9.
 113. Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 Study Group. Division of AIDS Treatment Research Initiative. *AIDS Res Hum Retroviruses* 1997;13:305–15.
 114. Mwamburi DM, Gerrior JL, Wilson IB, et al. Comparing megestrol acetate therapy with oxandrolone therapy for HIV-related weight loss: similar results in 2 months. *Clin Infect Dis* 2004;38:895–902.
 115. Liu L, Bopp MM, Roberson PK, Sullivan DH. Undernutrition and risk of mortality in elderly patients within 1 year of hospital discharge. *J Gerontol Med Sci* 2002;57A:M741–6.
 116. Sullivan DH, Walls RC. Protein-energy undernutrition and the risk of mortality within six years of hospital discharge. *J Am Coll Nutr* 1998;17:571–8.
 117. Sullivan DH, Yamashita BD, Johnson LE, et al. The GAIN (Geriatric Anorexia Nutrition Registry): The impact of appetite and weight on mortality in a long-term care population. *J Nutr Health Aging* 2002;6:275–81.
 118. Powell-Tuck J, Hennessy EM. A comparison of mid upper arm circumference, body mass index and weight loss as indices of undernutrition in acutely hospitalized patients. *Clin Nutr* 2003;22:307–12.
 119. Bruunsgaard H, Andersen-Ranberg K, Jeune B, et al. A high plasma concentration of TNF- α is associated with dementia in centenarians. *J Gerontol Med Sci* 1999;54A:M357–64.
 120. Dobbs RJ, Charlett A, Purkiss AG, et al. Association of circulating TNF- α and IL-6 with ageing and Parkinsonism. *Acta Neurol Scand* 1999;100:34–41.
 121. Kania DM, Binkley N, Checovich M, Havighurst T, Schilling, Ershler WB. Elevated plasma levels of interleukin-6 in postmenopausal women do not correlate with bone density. *J Am Geriatr Soc* 1995;43:236–9.
 122. Cohen HJ, Pieper CF, Harris T, et al. The association of plasma IL-6 levels with functional disability in community dwelling elderly. *J Gerontol Med Sci* 1997;52:M201–8.
 123. Catania A, Airaghi L, Motta P, et al. Cytokine antagonists in aged subjects and their relation with cellular immunity. *J Gerontol Biol Sci* 1997;52:B93–7.
 124. Larsson H, Elmstahl S, Gerglund G, Ahren B. Evidence for leptin regulation of food intake in humans. *J Clin Endocrinol Metab* 1998;83:4382–5.
 125. Morley JE, Kumar VB, Mattammal MB, Farr S, Morley PM, Flood JF. Inhibition of feeding by a nitric oxide synthase inhibitor: effects of aging. *Eur J Pharmacol* 1996;311:15–9.
 126. Morley JE, Alshaher MM, Farr SA, Flood JF, Kumar VB. Leptin and neuropeptide Y (NPY) modulate nitric oxide synthase: further evidence for a role of nitric oxide in feeding. *Peptides* 1999;20:595–600.
 127. Morley JE, Flood JF. Evidence that nitric oxide modulates food intake in mice. *Life Sci* 1991;49:707–11.
 128. Morley JE. Anorexia and weight loss in older persons. *J Gerontol Med Sci* 2003;58:131–7.
 129. Chapman IM, MacIntosh CG, Morley JE, Horowitz M. The anorexia of ageing. *Biogerontology* 2002;3:67–71.
 130. Wilson MM, Vaswani S, Liu D, Morley JE, Miller DK. Prevalence and causes of undernutrition in medical outpatients. *Am J Med* 1998;104:56–63.
 131. Morley JE, Kraenzle D. Causes of weight loss in a community nursing home. *J Am Geriatr Soc* 1994;42:583–5.
 132. Bosley BN, Weiner DK, Rudy TE, Granieri E. Is chronic nonmalignant pain associated with decreased appetite in older adults? Preliminary evidence. *J Am Geriatr Soc* 2004;52:247–51.
 133. Teno JM, Kabumoto G, Wetle T, Roy J, Mor V. Daily pain that was excruciating at some time in the previous week: prevalence, characteristics, and outcomes in nursing home residents. *J Am Geriatr Soc* 2004;52:762–7.
 134. Milne AC, Potter J, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database Syst Rev* 2002;(3):CD003288.
 135. Wilson MMG, Purushothaman R, Morley JE. Effect of liquid dietary supplements on energy intake in the elderly. *Am J Clin Nutr* 2002;75:944–7.
 136. Meier DE, Ahronheim JC, Morris J, Baskin-Lyons S, Morrison RS. High short-term mortality in hospitalized patients with advanced dementia—lack of benefit of tube feeding. *Arch Intern Med* 2001;161:594–9.
 137. Tokuda Y, Koketsu H. High mortality in hospitalized elderly patients with feeding tube placement. *Intern Med* 2002;41:613–6.
 138. Abuksis G, Mor M, Plaut S, Fraser G, Niv Y. Outcome of percutaneous endoscopic gastrostomy (PEG): comparison of two policies in a 4-year experience. *Clin Nutr* 2004;23:341–6.
 139. Sherman FT. Nutrition in advanced dementia—tube-feeding or hand-feeding until death? *Geriatrics* 2003;58:10–12.
 140. Klose J, Heldwein W, Rafferteder M, Sernetz F, Gross M, Loeschke K. Nutritional status and quality of life in patients with percutaneous endoscopic gastrostomy (PEG) in practice—prospective one-year follow-up. *Dig Dis Sci* 2003;48:2057–63.
 141. Teasell R, Foley N, McRae M, Finestone H. Use of percutaneous gastrojejunostomy feeding tubes in the rehabilitation of stroke patients. *Arch Phys Med Rehabil* 2001;82:1412–5.
 142. Yeh SS, Wu SY, Lee TP, et al. Improvement in quality-of-life measures and stimulation of weight gain after treatment with megestrol acetate oral suspension in geriatric cachexia: results of a double-blind, placebo-controlled study. *J Am Geriatr Soc* 2000;48:485–92.
 143. Morley JE. Orexigenic and anabolic agents. *Clin Geriatr Med* 2002;18:853–66.