Dietary and Pharmacological Management of Severe Catabolic Conditions

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Abstract: *Introduction:* Nutritional debilitation is among the most devastating and life-threatening complications of cancers and various chronic diseases. It arises from a complex interaction between the illness and the host. This process includes cytokine production, release of lipid-mobilizing and proteolysis-inducing agents and alterations in intermediary metabolism. As a result, many patients develop cachexia with progressive body fat and muscle tissue wasting with associated worsening of their clinical status and a lower quality of life. This review will provide up-to-date information about different pharmacological management of cachexia. *Findings:* Until recently, the 2 major options for pharmacological therapy have been either progestational agents or corticosteroids. However, knowledge of the mechanisms of cachexia has led to newer therapeutic interventions for treating several aspects of the syndrome. These include antiserotonergic agents, branched-chain amino acids, eicosapentanoic acid, melanocortin antagonists and antimyostatin agents—all of which act on the feeding-regulatory circuitry to increase appetite and inhibit illness-derived catabolic elements. *Conclusions:* Information from this review will guide health care providers in limiting weight loss and improve performance status of the cachectic patients through dietary and pharmacological therapy, with the hope that such approach would extend patients survival and improve their quality of life.

Key Indexing Terms: Cachexia; Chronic illness; Malnutrition; Anorexia; Pharmacological therapy. **[Am J Med Sci 2011;342(6):513–518.]**

Various cancers and chronic illnesses are associated with severe anorexia that leads to a state of progressive protein calorie malnutrition and eventually unintentional weight loss. It is estimated that half of all patients with cancer and 6.3% of hospitalized patients suffer from life-threatening complications secondary to undernutrition.[1,2] Furthermore, recent data reported that greater than 91% of subjects with chronic illnesses who were admitted to skilled care facilities were either malnourished or at risk of malnutrition.[3] In most cases, there is a linear relationship between the severity of the illness, its duration and the extent of the ensuing undernutrition. The ultimate result is a state of "Cachexia" that is characterized with severe body wasting, poor performance and ultimately death.[4]

In general, cachexia could be secondary to a functional inability to ingest or effectively assimilate nutrients, with either condition related to gastrointestinal tract (GI) dysfunction or treatment-related GI toxicity. Furthermore, cachexia could be considered as a multidimensional mal adaptation syndrome that encompasses a variety of alterations that range from physiologically excessive cytokine release[5] to behavioral changes that frequently lead to poor clinical outcomes and compromised quality of life.

This review aims to shed light on the various mechanisms that might be involved in the development of cachexia and the available nutritional and pharmacological treatments to tackle this potentially lethal condition.

PATHOPHYSIOLOGICAL MECHANISMS OF ANOREXIA

Several pathophysiological changes are implicated in weight lose among severely ill patients. However, recent data support the central role of various neuropeptides in precipitating cachexia through their effects on the hypothalamic-arcuate nucleus (HTAN). The HTAN is principally involved in the control of energy homeostasis in rodents, whereas the same hypothalamic area in humans is termed infundibular nucleus, Figure 1. The HTAN acts as the main relay station through which peripheral signals relate information regarding energy and adiposity status.[6] One of the most prominent anabolic effectors of the HTAN pathways is the circuit containing neuropeptide Y (NPY).[7] Recent data supported the role of NPY as an anabolic signaling molecule, with NPY gene expression and secretion of the NPY peptide in the hypothalamus increases during active depletion of body adipose tissues and/or reduced leptin/insulin signaling to the brain. Furthermore, injection of NPY into cerebral ventricles or even directly into the hypothalamus of rats potently stimulates food intake and attenuate energy expenditure, while at the same time inducing lipogenic enzymes in liver and white adipose tissue.[7]

Another equally important circuit effector is leptin, a hormone normally secreted by adipose tissue. The HTAN is a major site for transducing afferent input related to the body level of leptin and circulating cytokines into a neuronal response and eventually into behavioral responses through second-order neuronal signaling pathways, Figure 2.[8,9] Recent data demonstrated that the secretion of leptin can be induced by proinflammatory cytokines, especially tumor necrosis factor (TNF)-α resulting in "inflammatory hyperleptinemia." Although not fully understood, cytokine-induced hyperleptinemia might have a role in disease-associated anorexia and cachexia that often accompany neoplastic, chronic infectious and autoimmune diseases.[10]

An equally important pathophysiological mechanism of cachexia is the ubiquitin-proteasome system (UPS), which provides unique controls of many cellular processes by proteolytic and nonproteolytic means.[11] In general, proteolysis through the UPS is a rapid and effective method of degrading a specific cellular protein at a specific time and in response to a particular cellular signal or event. Furthermore, by controlling where a protein is degraded, the UPS can enhance the specificity and timing of proteolysis in both mitotic and nonmitotic cells.

Various cancers and chronic illnesses are followed by excessive production of proinflammatory cytokines [such as TNF-α, interleukin (IL)-1 and IL-6], which in turn initiate proteolysis through the UPS.[11] After the breakdown of proteins by the UPS to amino acids and small peptides, these byproducts are then converted by the liver to acute phase proteins, such as

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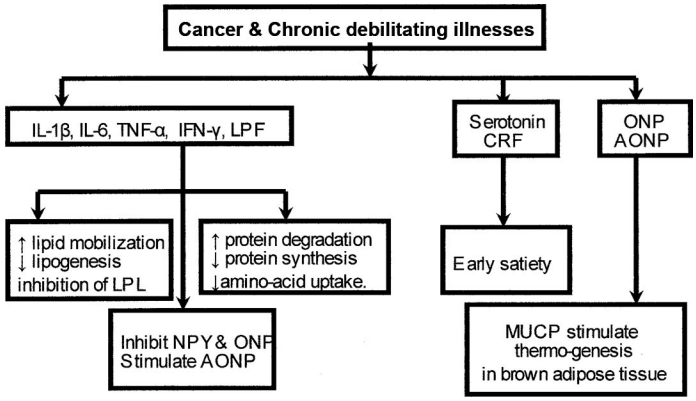

FIGURE 1. Pathogenic mechanisms of anorexia. NPY, neuropeptide Y; ONP, orexigenic neuropeptides; AONP, anorexigenic neuropeptides; VMH, ventromedial hypothalamus; MUCP, mitochondrial uncoupling protein. Lipoprotein lipase (LPL): the enzyme responsible for triglyceride clearance from plasma. Lipid-mobilizing factor (LPF): a cyclic adenosine monophosphate-dependent process. Adapted from Inui A. Cancer anorexia-cachexia syndrome: are neuropeptides the key? Cancer Res 1999; 59:4493–4501.

C-reactive protein, setting a vicious cycle that accelerates the loss of lean tissue mass through activating the UPS and the production of proinflammatory cytokines.[11]

Furthermore, cytokines halt the repair of muscles by inhibiting the activation of satellite cells in addition to initiating lipolysis with the release of triglycerides from adipose tissues.[7]

ASSESSMENT OF CACHEXIA

Nutritional status of severely ill patients is usually evaluated through a combination of clinical assessment and laboratory tests. The initial laboratory assessment should include evaluation for serum levels of albumin and other transport proteins.[12] In general, cachexia should be suspected if an involuntary weight loss of premorbid weight is observed of greater than 5% within 1 month or 10% over a 6-month period in combination with muscle wasting.[12] This is supported by a recent publication by Fearon et al,[13] who defined cachexia after evaluating 170 patients with advanced pancreatic cancer and proposed that cancer cachexia is characterized by 3 main elements: body weight loss $\geq$10%, nutrient intake $\leq$1500 kcal/d and level of C-reactive protein $\geq$10 mg/L.

NUTRITIONAL AND PHARMACOLOGICAL MANAGEMENTS

Undoubtedly, the obvious way to treat cachexia is to treat the underlying or precipitating illness and increase oral intake if possible. That can be initiated through structured nutrition screening to identify individuals at risk who may require a formal nutrition assessment in an attempt to minimize weight changes and identify individuals who may benefit from further nutrition counseling and other intervention.[14]

With respect to oral intake, frequent and small meals should be prescribed to avoid the negative consequences of chronic condition-related anorexia. Then the next therapeutic option would be to increase nutritional intake and to slow muscle and fat wasting by manipulating the metabolic milieu outlined above with a variety of nutritional supplements and pharmacological agents (Figure 2).

Enteral and Parenteral Nutritional Support

Patients on long-term antibiotics or chemotherapy may suffer from frequent stomatitis, vomiting and even chemotherapy-induced diarrhea, which severally limit achievement of

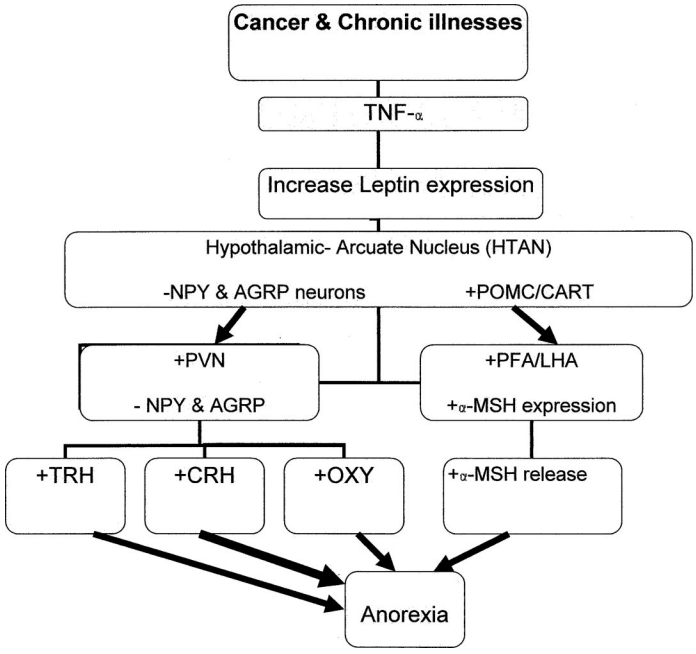

FIGURE 2. Leptin influences central satieties centers through its effects on HTAN followed by interaction with the second-order neuronal signaling pathways. HTAN, hypothalamic-arcuate nucleus; AGRP, agouti-related protein; POMC, proopiomelanocortin; CART, cocaine/amphetamine-regulated transcript; PVN, paraventricular nucleus; PFA, perifornical area; LHA, lateral hypothalamic area; NPY, neuropeptide Y; TRH, thyrotropin-releasing hormone; CRH, corticotropin-releasing hormone; OXY, oxytocin; MSH, melanin-releasing hormone. Adapted from Schwartz MW, Woods SC, Porte D Jr, et al. Central nervous system control of food intake. Nature 2000;404:661–671 and Finck BN, Johnson RW. Tumor necrosis factor-α regulates secretion of the adipocyte-derived cytokine, leptin. Microsc Res Tech 2000; 3:209–215.