

Cachexia in Cancer

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Severe, progressive malnutrition and wasting often is seen in advanced cancer, with weight loss long associated with decreased survival.¹ The term “cachexia” refers to a progressive weight loss with depletion of host reserves of skeletal muscle and adipose tissue. It also represents the complex and profound metabolic changes seen in advanced cancer, characterized by breakdown of skeletal muscle and abnormalities in fat and carbohydrate metabolism. Other important features of cachexia are anorexia, early satiety, muscle weakness, and fatigue.²

The syndrome, however, is not well defined. A recent consensus definition emphasizes the loss of fat and muscle and the complex metabolic changes.³ Diagnostic criteria are proposed, based on a weight loss of 5% or more in 12 months or less, plus at least three out of five of the following:

- Decreased muscle strength
- Fatigue
- Anorexia
- Low fat-free mass index
- Abnormal biochemistry (inflammatory markers, anemia, and low albumin)

Another proposed three-factor classification emphasizes that patients with weight loss, reduced food intake, and evidence of systemic inflammation are particularly at risk in terms of adverse functional status and prognosis, and that such patients should receive evaluation for intervention as soon as identified.⁴

The Two Pathways to Wasting

The development of cachexia reflects both a reduced food intake and a catabolic metabolism induced by an inflammatory host response to tumor presence and/or tumor factors.⁵ This leads to a negative energy and protein balance, manifesting as weight loss as body stores are progressively depleted. Because low food intake, for whatever reason, is in one pathway only, stand-alone nutritional intervention is unlikely to correct the imbalance, unless the metabolic changes are addressed at the same time.⁶

Energy Balance in Cancer Cachexia

When food intake is lower than requirements, body energy stores are mobilized to meet demands. This is normally a metabolic and behavioral adaptation, leading to decreased energy expenditure. Furthermore, body fat stores are preferentially used for fuel, with a relative sparing of the fat-free body mass. In cancer cachexia with systemic inflammation, activation of protein breakdown in skeletal muscle is seen, and the amino acids thus generated are used to fuel hepatic protein and glucose synthesis.⁷ Thus, faster breakdown of skeletal muscle occurs with a preservation of visceral organs. Nutrition support is capable of restoring body fat, but muscle breakdown still is driven by systemic inflammation.

Negative energy balance leading to progressive weight loss is attributed to changes in energy intake, components of energy expenditure, or both, mediated by metabolic alterations.

Diminished food intake is a prominent feature in weight-losing cancer patients, with most, but not all, studies reporting a low intake. We found a low intake in 297 patients with advanced cancer, mainly gastrointestinal tumors.⁸ Mean dietary intake was below maintenance requirements, but not different in normometabolic and hypermetabolic patients. Weight loss

of more than 10% was present in 43% of the patients and elevated resting energy expenditure (REE) in 48%. Weight loss was not accounted for by diminished dietary intake, because energy intake in absolute amounts was not different and intake per kilogram body weight was higher in weight-losing patients compared to weight-stable patients. Increased REE could make a large contribution to negative energy balance, if not compensated for by an increase in energy intake.

Thus, metabolic derangements contribute to cachexia development, and these metabolic changes differ from those induced by decreased energy intake or starvation alone.

Body Composition in Cancer Cachexia

In simple starvation, muscle mass usually is preserved at the expense of body fat depots, which are preferentially used to provide energy. In contrast, relatively more muscle tissue is lost in the development of cancer cachexia, and these changes are not reversed if adequate energy and other nutrients are provided, as seen in “pure” starvation states. The active body cell mass (predominantly skeletal-muscle tissue) and its associated intracellular water decrease, while the extracellular space is maintained or more slowly decreased, with or without clinical signs of edema. Thus, body weight changes may not accurately reflect the amount of muscle and fat lost.⁹ To better characterize the depletion of cancer cachexia, expansion is needed of the commonly used body mass index (BMI) in order to reflect these body composition changes, for instance using height-adjusted indices of fat-free mass index (FFMI), fat mass index (FMI), and skeletal muscle index (SMI). However, this requires defined reference values and standardized body composition measurements.¹⁰

Nutrition Support

The best way to treat cancer cachexia is obviously to cure the cancer, thus normalizing the metabolic abnormalities induced by the tumor and/or tumor/host interactions. When cure is unachievable, an obvious next option is to increase nutritional intake by dietary counseling and oral nutritional supplements or by artificial nutrition. A number of studies have tried to achieve this. However, no benefits were found in terms of anthropometric measures, response rate to therapy, survival, or quality of life.¹¹

Parenteral nutrition is difficult to supply over extended periods of time and is associated with a number of complications. A number of earlier, mostly parenteral, nutrition trials have shown no benefit, but rather a tendency to increase infectious complications.¹¹ Thus, no evidence exists to show that increased nutritional intake alone is effective in the palliation of cancer cachexia.

Anticatabolic Therapy

The disappointing results of stand-alone conventional nutritional supplementation in cancer patients has led to a focus on the metabolic changes in cancer cachexia and attempts to manipulate the metabolic alterations with a variety of pharmacological agents. Thus, it seems that strategies to counteract the inflammatory response and its metabolic consequences are an option.

Steroids are widely used and are shown to improve appetite. However, steroids will not reverse ongoing weight loss and muscle wasting, their symptomatic benefits are often short-lived, and they are associated with a number of adverse effects. Nonsteroidal anti-

inflammatory drugs (NSAIDs) are shown to reduce acute-phase proteins and resting energy expenditure (REE), and preserve body fat in patients with advanced cancer.¹² Treatment with indomethacin is shown to stabilize performance status and prolong survival.¹³ Therefore, NSAIDs seem to have a role in the palliation of cancer cachexia, although effect size and response rate still are not well known.

Anabolic androgenic steroids stimulate net muscle protein synthesis, with testing in a number of catabolic conditions, but their therapeutic potential in cancer cachexia is largely unknown.⁶ Much interest also has focused on the importance of the growth hormone (GH)/insulin-like growth factor (IGF-1) axis on the anabolic regulation of skeletal muscle mass. However, in cancer patients, the ongoing worry remains that growth factors may stimulate tumor growth, and these concerns may limit trials in this area.

We recently have shown that low-dose insulin treatment (0.11 ± 0.05 units/kg/day) stimulated carbohydrate intake and metabolic efficiency during exercise, and improved survival in cancer cachexia.¹⁴ However, fat-free mass, maximum exercise capacity, and spontaneous physical activity were unaffected.

The role of treatments to reverse the underlying metabolic changes in cancer cachexia is presently unclear.

Multimodal Approach

We have studied the effect of nutritional support in combination with anti-inflammatory treatment (NSAID) and anemia prevention (erythropoietin) in 309 patients with progressive cachexia because of solid tumors.¹² As-treated analysis demonstrated that patients receiving

nutritional support had a prolonged survival, accompanied by improved energy balance, body fat, and a greater maximum exercise performance. The results support that nutrition is a limiting factor influencing survival and that treatment targeted toward both diminished nutritional intake and metabolic alterations is perhaps more effective. A recent study of patients on palliative chemo/radiotherapy given oral nutrition support plus parenteral nutrition (30% of requirements) also showed improved 48-week survival, body composition, and quality of life.¹⁵

Perspectives

The metabolic alterations in advanced cancer have many parallels to a chronic systemic inflammatory response and differ considerably from the metabolic changes in starvation. Nutritional support alone does not appear to affect overall survival in advanced cancer, but in combination with treatment targeted against the inflammatory response and/or metabolic abnormalities, focusing also on energy expenditure is possibly of greater value. Therapeutic strategies aimed at modulating the mediators of the catabolic response, such as cytokines and eicosanoids, or metabolic regulation, such as with anabolic and anticatabolic agents, may thus offer more promise in the future. Early detection and intervention also may prove more effective. An optimal therapeutic approach to cancer cachexia is not yet available. Strategies to counteract both catabolism and reduced dietary intake may have importance for the survival, function, and quality of life of cancer patients, and researchers should continue to explore this in interventional studies.

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