

## The Role of Nutritional Supplements in the Treatment of Cachexia in Cancer Patients—The Registered Dietician’s Perspective

a report by

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An appreciation of nutritional support as a critical component of the continuum of cancer care has only recently emerged, bolstered by recent studies showing that support is critical not only to the maintenance of lean body mass (LBM), weight, and performance status and their impact on quality of life (QoL), but also to tolerance and completion of treatment itself.<sup>1</sup>

Only a generation ago, nutritional interventions were largely neglected and were begun late, if ever, due to theoretical concerns that nutritional support would ‘feed the tumor.’ This regrettably left a starved host as the unspoken alternative. Not until 1980 was the detrimental impact of malnutrition first quantified through an evaluation of 12 Eastern Co-operative Oncology Group trials that documented the poor prognosis associated with an unplanned weight loss of as little as 5%.<sup>2</sup> However, widespread efforts to improve nutritional support for patients were not immediately implemented since many felt weight loss was merely an unavoidable consequence of aggressive disease. Almost two decades later, Andreyev offered an alternative explanation, exposing the fact that those with weight loss actually received less treatment.<sup>3</sup> These patients developed more toxicity, resulting in dose reduction and abbreviated treatment courses. They had significantly lower QoL and performance status, poor response to treatment, and reduced overall survival. Yet, for those whose weight could be stabilized, survival was significantly improved—an observation confirmed by more recent studies.<sup>4,5</sup> Other research has shown that, while nutritional deterioration was related to disease status, reduced energy and protein intakes and weight loss were also independently associated with impaired QoL. An emerging area of research, QoL has always been a prime concern of cancer patients themselves.<sup>1,6,7</sup>

This article will focus on the role of the registered dietician (RD) on the oncology team, identifying and implementing therapeutic nutritional interventions that both effectively stabilize weight and maintain and

rebuild LBM. Planning effective strategies entails triaging patients to determine the source of their weight loss, allowing the team to target the specific underlying factors. Ultimately, there must be differentiation between patients experiencing symptom-related weight loss and those with metabolic abnormalities that define cachexia.

### Calories, Protein, and Lean Body Mass

Adequate calories to provide the energy needed for normal function is the body’s top priority, and protein will be burned as energy when calories are grossly inadequate—a common consequence of cancer and treatment-related symptoms such as anorexia, taste changes, and early satiety. These symptoms are present in up to 80% of patients with gastrointestinal (GI) tumors and 60% of lung cancer patients, but much less frequently with breast or hematological malignancies.<sup>8</sup>

Muscle/LBM is directly affected by protein intake in the diet, replenishing the amino acids lost during the fasting state between meals. Optimal intake that supports muscle function is estimated at 1.8g protein/kg/day; this is met by the average American diet, but protein is one of the most common deficits when intake is limited.<sup>9</sup> Exercise also improves function, with the most benefit from early interventions to limit loss of LBM.

The stressed state seen in advanced cancer results in far greater demand for amino acids released from muscle breakdown than occurs in fasting alone.<sup>10</sup> When dietary protein is not spared or is inadequate in the diet, muscle catabolism provides the amino acids to maintain the protein mass of critical organs and tissues. It is also used to maintain normal plasma glucose concentration, which ensures energy is available to essential organs. In addition, muscle reserves support the production of other critically essential proteins—i.e. albumin—though typically at suboptimal levels for conservation of LBM. The consequences of protein deficits are quickly exhibited as fatigue, delayed healing, poor immune response, and declining ability to maintain normal activities due to loss of LBM. When 40% of these critical protein reserves are exhausted, mortality approaches 100%, typically due to pneumonia/infection.

Loss of muscle mass is known to be detrimental in cancer and has been shown to predict recurrence and reduce survival.<sup>11</sup> Patients with increased risk of loss of LBM include those with solid tumors—such as lung, pancreatic, gastric, or head and neck cancers—or those with advanced hematopoietic disease. Cachexia is associated with increased losses due to increased muscle degradation stimulated by pro-inflammatory cytokines.<sup>12</sup>



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**Nutritional Solutions/Supplements for Symptom-related Weight Loss**

Several useful resources are available outlining the baseline assessments, ongoing surveillance, high calorie interventions, and patient education needed to address the symptoms limiting oral intake.<sup>13,14</sup> These offer the RD effective treatment strategies when weight loss is clearly proportionate to calorie deficit and weight losses are primarily from fat stores. Interventions include:

- addressing barriers to eating, such as nausea, diarrhea, mucositis, reflux, and depression;
- establishing a schedule with small, frequent meals and snacks;
- maximizing caloric density; and
- using fluids with calories, including oral nutritional supplements.

The use of fluids with calories is a critical component, since their consumption requires less effort than is needed for chewing/swallowing solid foods, they rarely stimulate the gag reflex, and may speed gastric emptying, resulting in fewer complaints of early satiety. When volumes are limited, calorie-containing fluids are essential in meeting both hydration and calorie goals. Options include commercially produced products and homemade recipes. The key is helping the patient find supplements that he/she can tolerate and willingly consume. Incorporating variety can prevent the otherwise inevitable ‘burn-out.’

Enteral or, less commonly, parenteral nutrition support has been shown to be beneficial when voluntary oral intake fails, primarily in a subset of malnourished patients anticipating major surgery or bone marrow transplant, or for those experiencing a prolonged period of GI toxicities, such as with head and neck cancer patients.

**Nutritional Solutions/Supplements for Tumor-mediated Cachexia**

Although weight loss in cachexia is often attributed to anorexia, it involves more than a simple caloric deficit and can occur in the absence of anorexia.<sup>15</sup> The energy deficit, if any, does not account for the amount of muscle mass and weight that is lost, often early in the disease course. Skeletal muscle and fat are lost at almost equivalent rates, impacting strength and QoL.

Tumor-related metabolic factors create changes in the metabolism of protein, carbohydrate, and fat that result in muscle wasting, which can precede any decline in intake. Targets for anticachectic therapies have included:

- proteolysis-inducing factor (PIF), which is responsible for targeting muscle mass for degradation, leading to extensive loss of LBM;
- lipid-mobilizing factor, leading to increased lipid breakdown and energy losses through thermo genesis; and
- cytokine-triggered inflammatory response: tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1, IL-6.

Detailing these factors and their implications for nutritional status are beyond the scope of this article, but they have been reviewed elsewhere.<sup>14,16</sup>

Nutritional counseling and the addition of traditional oral supplements did not improve weight in Ovesen’s study of cachectic patients.<sup>17</sup> Appetite stimulants have been shown to improve weight, but were ineffective in increasing LBM. Only eicosapentaenoic acid (EPA)-containing oral supplements (ProSure, Resource Support) or the combination of B-hydroxy-B-methyl butyrate (HMB), arginine, and glutamine (as Juven) have been shown to block mediators of cachexia, with resulting gains in both weight and skeletal muscle mass. Compared with the progressive weight loss that is predictable in pancreatic cancer patients, those consuming two cans of ProSure daily were able to gain weight slowly,<sup>18</sup> though the increased caloric intake alone could not mathematically account for the change in weight; further analysis confirmed that the improvement came from better metabolic efficiency.<sup>19</sup> The caloric discrepancy was also seen in cancer patients drinking two servings of Juven daily, with gains of 2.5lb LBM compared with a loss of 2.9lb in controls. This net difference of 5.4lb muscle mass developed over only four weeks, although the Juven group actually consumed fewer total calories and less protein.<sup>20</sup>

Assessing patients for loss of muscle mass is frequently overlooked by dietitians as it has typically been ignored in our formal education, but it is essential to our decision-making with regard to cancer patients.

The combination of oral supplements with individual counseling is the most effective therapy...

Realistically, the required equipment is frequently unavailable even for those trained in bioelectrical impedance analysis or other methods used to directly measure LBM. In spite of this, losses of LBD can be accurately documented and even predicted by screening for the predictors and physical penalties associated with this loss, including:

- rapid weight loss of >2lb per week, accompanied by the additional predictors detailed below;
- visible losses of muscle mass, such as temporal wasting or wasting of arm/leg muscle—a video demonstrating physical assessment as part of a patient-generated subjective global assessment (PGSGA) is available through the American Dietetics Association;<sup>21</sup>
- weakness, with loss of strength;
- fatigue, as protein reserves are less able to stabilize blood sugar levels;
- decreases on performance or functional status scales; and

- alterations in serum proteins with an elevated C-reactive protein and declines in albumin levels.

## Nutritional Counseling Improves Outcomes

Despite strong research linking poor nutritional status with negative outcomes of cancer therapy, almost half of the patients in a 2004 survey said they did not receive any nutritional counselling.<sup>22</sup> Several recent studies have shown that nutritional counseling statistically improved protein and calorie intake, nutritional status, weight, physical function, and QoL.<sup>23–25</sup> Ravasco's research comparing individual counseling, oral supplements alone, and usual care/controls found statistical improvement in caloric and protein intakes, weight, nutritional status, function, and QoL in dietician-counseled patients. The individually counseled group maintained their gains for three months after completion of radiation therapy, without further counseling. The oral supplement group alone had improvements during the study, but the benefits were not sustained three months later. The control group lost ground throughout.<sup>25</sup>

Individualized, sequential counseling takes into account personal preferences and patterns and addresses specific barriers to intake. Oral supplements in isolation temporarily increased intake but did not sustain that improvement over time, possibly due to the taste fatigue that can develop with repeated consumption or, alternatively, due to unaddressed barriers. The fact that any weight gain was achieved is counter to an earlier study<sup>17</sup> and may reflect the cancer-specific QoL scale used in the recent studies, or improvements in the oral supplements available or in the quality and frequency of nutritional counseling.

Ideally, the combination of oral supplements with individual counseling is the most effective therapy, with periodic counseling to sustain interventions that are working for the patient while addressing any new barriers that arise. Certainly, oral supplements are an integral part of the practice of most oncology dietitians, with the most successful interventions including a manipulation of everyday foods, rotation of oral supplements, and management of symptoms that interfere with eating. Identifying the

appropriate supplement for each patient has always been our responsibility, and options that target metabolic abnormalities offer new tools.

## Recommendations on the Appropriate Use of Supplements in Cachexia

Identifying and targeting the appropriate supplement for oral use or as tube feeding will vary with the presence or absence of cachexia. Where patients are achieving adequate caloric intakes without the anticipated stabilization of

Specialized nutritional supplements are warranted in cachectic patients and may limit significant losses of lean body mass that would otherwise undermine these vital goals.

weight, specialized formulas that address the metabolic changes of cachexia should be trialed. In this setting, I have found that isocaloric substitutions of ProSure or Resource Support in tube feedings or as oral supplements have often eliminated further weight loss. Likewise, Juven has been beneficial where loss of muscle mass was the critical factor, maintaining LBM even when caloric intake was less than optimal. Though personal experience is anecdotal, the clear survival benefit of weight stabilization is not,<sup>3–5</sup> and mandates more randomized studies to identify optimal nutritional interventions that can be initiated early in the treatment course of our patients.

An integrated approach to cancer management must include nutritional support to optimize nutritional status, using strategies to preserve the protein stores that impact functional status, tolerance of therapy, and QoL. Specialized nutritional supplements are warranted in cachectic patients and may limit significant losses of LBM that would otherwise undermine these vital goals. ■

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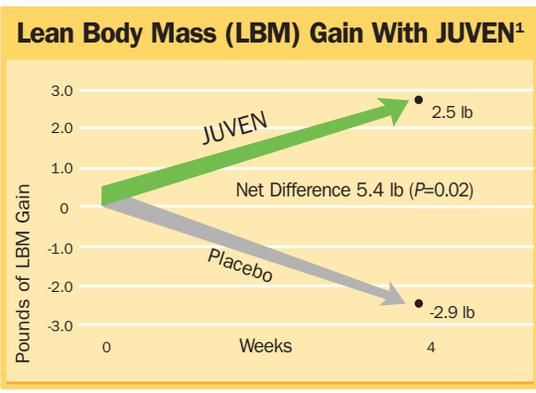


Chart developed from information in May PE et al: *Am J Surg* 2002;183:471-479.

In this double-blind study, patients (N=49) with advanced solid tumors (stage IV) and >5% weight loss were randomized to receive JUVEN BID or a nitrogen content-matched nutrient mixture BID.

- JUVEN patients gained more LBM despite taking in fewer calories and less protein\*<sup>1</sup>
  - 32% fewer calories/day than the control group (1487 Cal/day vs 2169 Cal/day)
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- JUVEN patients continued to gain LBM throughout the 24-week study<sup>1</sup>

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\*Reported in dietary intake questionnaire after first 4 weeks. † Data analyzed by ITT repeated measures ANOVA and adjusted using baseline observation as a covariant. The quadratic contrast of treatment on time was significantly different over the 24 weeks (P=0.02). ‡ β-hydroxy-β-methylbutyrate. 1. May PE et al: *Am J Surg* 2002;183:471-479. 2. Knitter AE: *J Appl Physiol* 2000;89:1340-1344. 3. Nissen S: *J Appl Physiol* 1996;81:2095-2104. 4. Barbul A: *Surgery* 1990;108:331-337. 5. Kirk et al: *Surgery* 1993;114:155-160. 6. Souba WW: *JPEN* 1985;9:608-617.

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