



## The Role of Branched-Chain Amino Acids and Eicosapentaenoic Acid in Improving Body Composition and Functional Capacity in Nasopharyngeal Carcinoma Patients with Cancer Cachexia: A Case Report

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### ABSTRACT

**Introduction:** Cancer cachexia is a debilitating syndrome characterized by involuntary weight loss, muscle wasting, and functional decline, negatively impacting quality of life and survival. Nutritional interventions, including branched-chain amino acids (BCAAs) and eicosapentaenoic acid (EPA), have shown promise in ameliorating cachexia. This case report illustrates the potential benefits of these nutrients in a patient with nasopharyngeal carcinoma. **Case presentation:** A 65-year-old female presented with severe fatigue, dysphagia, and significant weight loss (11 kg in 6 months) secondary to nasopharyngeal carcinoma (T1N3Mx, stage IV). She was diagnosed with cancer cachexia and severe malnutrition. Nutritional therapy included enteral nutrition with 1.5-2 g/kgBW/day protein, 11-12 g/day BCAAs, and 1-2 g/day EPA. **Conclusion:** This case report suggests that a nutritional approach combining high protein, BCAAs, and EPA may improve body composition and functional capacity in patients with cancer cachexia. Further research is warranted to confirm these findings in larger studies.

### 1. Introduction

Cancer, a relentless adversary in the realm of human health, casts a formidable shadow in the form of cachexia—a multifactorial syndrome that ravages the body's nutritional status and functional capacity. Affecting a substantial proportion of cancer patients, particularly those in advanced stages, cachexia is a sinister harbinger of morbidity and mortality, undermining the therapeutic efficacy of oncologic interventions and diminishing the quality of life for those already grappling with the burden of malignancy. Characterized by a constellation of devastating symptoms, including involuntary weight

loss, muscle wasting, anorexia, fatigue, and metabolic dysregulation, cancer cachexia represents a complex interplay of biological, physiological, and psychological factors that conspire to dismantle the intricate tapestry of homeostasis. This intricate web of pathophysiological mechanisms is driven by a multitude of tumor-derived factors, inflammatory cytokines, and hormonal imbalances that collectively disrupt the delicate balance of energy metabolism, protein turnover, and nutrient utilization. The relentless catabolic state that defines cancer cachexia precipitates a cascade of deleterious consequences. Muscle wasting, a hallmark of the syndrome, not only



compromises physical function and independence but also exacerbates fatigue and impairs the ability to tolerate and respond to cancer therapies. Anorexia, the profound loss of appetite that often accompanies cachexia, further exacerbates the nutritional deficit, perpetuating a vicious cycle of malnutrition and metabolic derangement.<sup>1,2</sup>

The intricate pathophysiology of cancer cachexia underscores the critical importance of comprehensive management strategies that address the multidimensional nature of this devastating syndrome. While oncologic therapies remain the cornerstone of cancer treatment, their efficacy is often compromised by the presence of cachexia, highlighting the urgent need for adjunctive interventions that can mitigate the deleterious effects of this metabolic malady. Nutritional interventions have emerged as a promising avenue for ameliorating the burden of cancer cachexia. Recognizing the pivotal role of adequate nutrition in maintaining physiological function and supporting the body's resilience against disease, a growing body of evidence suggests that targeted nutritional strategies can positively impact body composition, functional capacity, and overall quality of life in cancer patients. Among the myriad nutritional interventions under investigation, the potential benefits of branched-chain amino acids (BCAAs) and eicosapentaenoic acid (EPA) have garnered significant attention in recent years. BCAAs, essential amino acids that cannot be synthesized *de novo* by the human body, have been shown to play a pivotal role in muscle protein synthesis and metabolism. These unique amino acids, namely leucine, isoleucine, and valine, serve as critical building blocks for muscle tissue and exert potent anabolic effects by stimulating protein synthesis pathways and inhibiting protein degradation.<sup>3,4</sup>

The therapeutic potential of BCAAs in cancer cachexia stems from their ability to counteract the catabolic processes that drive muscle wasting. Numerous preclinical and clinical studies have

demonstrated the efficacy of BCAA supplementation in attenuating muscle loss, improving muscle strength, and enhancing functional capacity in cancer patients. Moreover, BCAAs have been shown to modulate inflammatory responses, reduce oxidative stress, and improve insulin sensitivity, further contributing to their therapeutic potential in this complex syndrome. Eicosapentaenoic acid (EPA), an omega-3 fatty acid found abundantly in fatty fish and fish oil, has also emerged as a promising nutritional agent in the management of cancer cachexia. EPA exerts potent anti-inflammatory effects by modulating the production of pro-inflammatory cytokines and eicosanoids. By mitigating the inflammatory milieu that often accompanies cancer and its therapies, EPA may help to preserve muscle mass, improve appetite, and enhance overall nutritional status. Furthermore, EPA has been shown to promote the synthesis of anti-inflammatory mediators, such as resolvins and protectins, which actively participate in the resolution of inflammation and tissue repair. These pleiotropic effects of EPA, coupled with its ability to modulate lipid metabolism and improve insulin sensitivity, underscore its potential as a multi-faceted therapeutic agent in cancer cachexia.<sup>5,6</sup>

The synergistic potential of combining BCAAs and EPA with high-protein nutrition in the management of cancer cachexia represents a compelling avenue for further investigation. By addressing the underlying mechanisms of muscle wasting, inflammation, and metabolic dysregulation, this integrated approach may offer a comprehensive and effective strategy for mitigating the deleterious consequences of this debilitating syndrome.<sup>7,8</sup> This case report aims to shed light on the potential benefits of such a nutritional intervention in a patient with nasopharyngeal carcinoma and cancer cachexia. By meticulously documenting the clinical course and response to therapy, this report contributes to the growing body of evidence supporting the role of targeted nutrition in improving outcomes for cancer patients.



## 2. Case Presentation

A 65-year-old female patient presented to the clinical nutrition clinic RSCM on August 24<sup>th</sup>, 2023, with the main complaint fatigue has been getting worse since 2 months ago. Complaints accompanied by difficulty chewing and swallowing solid food. decreased sense of smell and taste, decreased appetite, and weight loss of 11 kg in 6 months. During the last 2 months, all personal activities were assisted, and the patient mostly lay in bed. Six months ago the patient complained of double vision accompanied by complaints of left facial numbness, dizziness, left ear feeling full, and ringing. The patient went to the neurology clinic RSCM and underwent an MRI examination with the results showing a tumor in the nasopharynx. Upon examination in the clinical nutrition clinic, the patient was moderately ill and conscious with the Glasgow Coma Scale (GCS) of E4M6V5. Vital signs included a blood pressure of 140/90 mmHg, pulse rate of 84 beats/minute, respiratory rate of 20 breaths/minute, temperature of 36.5 degrees Celsius, and oxygen saturation of 99% on room air. Anthropometric examination showed that the body weight was 54,6 kg, height 149 cm, and body mass index 24,6 kg/m<sup>2</sup>. From the physical examination, there was ptosis of the left eyelid, left and right eyeballs deviated medially, and impression of left N III and N VI paresis bilaterally. The patient had a

silicone nasogastric tube installed and muscle wasting was visible in both lower extremities. From body composition examination fat mass 45% (very high), muscle mass 18.3% (low), visceral fat 9.5 L (normal), subcutaneous fat 34.8%, FFMI 13.5 kg/m<sup>2</sup> (low). The result from the handgrip examination from the right hand was 10,5 kg and from the left hand was 10,2 kg.

The laboratory results of this patient were Hemoglobin 15.2 g/dL, leucocyte 12790/μL, thrombocyte 165000/μL, sodium 136 mEq/L, potassium 3.5 mEq/L, albumin 3.6 g/dL, blood glucose 92 mg/dL, urea 27.8 mg/dL, creatinine 0.8 mg/dL, estimated glomerular filtration rate 77.6 mL/min/1.73m<sup>2</sup>. The primary diagnosis was clinically severe malnutrition and cancer cachexia in nasopharyngeal carcinoma T1N3Mx stage IV pro chemoradiotherapy and Horner syndrome. Patients are given protein at 1.5-2 g/kgBW/day, enteral nutrition containing branched-chain amino acid (BCAA) 11-12 g/day, and eicosapentaenoic acid (EPA) 1-2 g/day as part of nutritional therapy for 30 days. Patients were monitored weekly for changes in body weight, fat mass composition, muscle mass composition, and functional capacity. From the monitoring results, it was found that body composition examination results had improved from the initial visit to the 4th visit as shown in Figure 1.



Figure 1. Changes in body composition.



Providing optimal protein will support the formation of the patient's muscle mass, and increase functional capacity and quality of life. After one month

of giving protein at 1.5-2 g/kgBW/day, apart from improving body composition, the patient's grip strength also increased as shown in Table 1.

Table 1. Handgrip examination.

	<b>Right (kg)</b>	<b>Left (kg)</b>
Initial assessment	10.5	10.2
Monitoring 1 (with NGT)	18	17.8
Monitoring 2 (with NGT)	18.3	18.1
Monitoring 3 (with NGT)	18.6	18.4

NGT: nasogastric tube.

### 3. Discussion

The presented case serves as a microcosm, encapsulating the multifaceted challenges and potential solutions associated with cancer cachexia. This debilitating syndrome, a frequent companion of advanced malignancies such as nasopharyngeal carcinoma, imposes a substantial burden on patients, eroding their quality of life, impairing their functional capacity, and jeopardizing the effectiveness of oncologic therapies. The patient's profound weight loss, muscle wasting, and fatigue, despite standard cancer treatment, underscore the insidious nature of cachexia and the urgent need for targeted interventions. The multifaceted pathophysiology of cancer cachexia is a testament to the intricate interplay between tumor biology, systemic inflammation, hormonal dysregulation, and metabolic derangement. The relentless catabolic state that characterizes this syndrome is fueled by a complex cascade of molecular events involving pro-inflammatory cytokines, tumor-derived factors, and altered neuroendocrine signaling. These mediators collectively disrupt energy homeostasis, promote muscle protein breakdown, and suppress appetite, culminating in a vicious cycle of malnutrition and functional decline. In this intricate landscape, nutritional interventions have emerged as a beacon of hope, offering the potential to mitigate the deleterious consequences of cachexia and improve patient outcomes. The rationale for nutritional therapy in this context is rooted in the understanding that adequate

nutrition is not merely a passive bystander but an active participant in the body's defense against disease. By providing the essential building blocks for tissue repair, immune function, and metabolic homeostasis, nutrition can fortify the body's resilience and enhance its ability to cope with the physiological stresses imposed by cancer and its treatments.<sup>9,10</sup>

The nutritional intervention implemented in this case, encompassing high protein intake, branched-chain amino acids (BCAAs), and eicosapentaenoic acid (EPA), represents a multi-pronged approach designed to address the diverse pathophysiological mechanisms underlying cancer cachexia. Each component of this intervention plays a distinct yet complementary role in mitigating the catabolic processes, restoring nutritional balance, and improving functional capacity. High protein intake is a cornerstone of nutritional therapy for cachexia. Protein, composed of essential amino acids, is the fundamental building block for muscle tissue. In the context of cachexia, where muscle wasting is a cardinal feature, ensuring adequate protein intake is paramount for preserving lean body mass, promoting muscle protein synthesis, and counteracting the catabolic forces that drive muscle breakdown. Branched-chain amino acids (BCAAs) are a unique subset of essential amino acids that have garnered considerable attention for their potential therapeutic applications in cancer cachexia. Leucine, isoleucine, and valine, the three BCAAs, exhibit potent anabolic properties, stimulating muscle protein synthesis through the activation of the mTOR



signaling pathway. This intricate network of intracellular signaling molecules plays a central role in regulating protein translation and cellular growth, making it a prime target for therapeutic interventions aimed at promoting muscle anabolism. In addition to their anabolic effects, BCAAs have been shown to exert anti-catabolic properties by inhibiting the ubiquitin-proteasome system, a major pathway responsible for protein degradation in muscle tissue. This dual action of BCAAs, promoting protein synthesis while suppressing protein breakdown, makes them a valuable tool for mitigating muscle wasting and preserving lean body mass in cancer cachexia.<sup>10,11</sup>

Furthermore, BCAAs have been implicated in modulating inflammatory responses, reducing oxidative stress, and improving insulin sensitivity, all of which are relevant in the context of cancer cachexia. Inflammation, a hallmark of cancer and its treatments, can exacerbate muscle wasting and contribute to metabolic dysregulation. BCAAs have been shown to attenuate the production of pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), thereby mitigating the inflammatory milieu that perpetuates cachexia. Oxidative stress, another key player in the pathogenesis of cachexia, arises from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defenses. BCAAs have been shown to enhance antioxidant capacity, protecting cells from oxidative damage and preserving cellular function. Moreover, BCAAs can improve insulin sensitivity, a crucial factor in glucose metabolism and energy homeostasis. By enhancing insulin signaling, BCAAs may help to mitigate insulin resistance, a common feature of cancer cachexia, and improve glucose utilization in muscle tissue.<sup>11,12</sup>

Eicosapentaenoic acid (EPA), an omega-3 fatty acid renowned for its anti-inflammatory properties, adds another dimension to the nutritional intervention in this case. EPA exerts its effects by modulating the production of eicosanoids, bioactive lipid mediators

derived from arachidonic acid. By competitively inhibiting the enzymes involved in arachidonic acid metabolism, EPA reduces the synthesis of pro-inflammatory eicosanoids, such as prostaglandins and leukotrienes, and promotes the formation of anti-inflammatory resolvins and protectins. This shift in the eicosanoid profile has profound implications for the inflammatory milieu in cancer cachexia. By mitigating inflammation, EPA may help to preserve muscle mass, improve appetite, and enhance overall nutritional status. Furthermore, EPA has been shown to promote the synthesis of anti-inflammatory cytokines, such as interleukin-10 (IL-10), which actively counteracts the pro-inflammatory cascade that contributes to cachexia. In addition to its anti-inflammatory effects, EPA has been implicated in modulating lipid metabolism, improving insulin sensitivity, and enhancing mitochondrial function. These pleiotropic effects of EPA, coupled with its ability to modulate neuroendocrine signaling, further reinforce its potential as a therapeutic agent in cancer cachexia. The combined use of BCAAs and EPA in this case represents a synergistic approach that leverages the unique properties of each nutrient to address the multifactorial nature of cachexia. The anabolic effects of BCAAs, coupled with the anti-inflammatory and metabolic benefits of EPA, provide a comprehensive strategy for mitigating muscle wasting, improving nutritional status, and enhancing functional capacity.<sup>13,14</sup>

The positive clinical outcomes observed in this case, including the improvement in body composition (increased muscle mass, decreased fat mass) and functional capacity (improved grip strength), provide preliminary evidence supporting the efficacy of this nutritional intervention. While this is a single case report, the findings are consistent with previous studies that have investigated the role of BCAAs and EPA in cancer cachexia. However, it is important to acknowledge the limitations of this case report. The small sample size and lack of a control group preclude



definitive conclusions about the efficacy of the intervention. Further research, including randomized controlled trials, is warranted to confirm these findings in a larger population and to elucidate the optimal dosing and duration of therapy. Delving deeper into the molecular mechanisms underlying the effects of BCAAs, it is imperative to acknowledge the pivotal role of leucine, often hailed as the "trigger" for muscle protein synthesis. Leucine exerts its anabolic effects by activating the mechanistic target of the rapamycin (mTOR) signaling pathway, a complex network of intracellular kinases that orchestrates protein translation and cellular growth. Upon entering the cell, leucine binds to the leucine-sensing protein Sestrin2, which in turn disinhibits the mTOR complex 1 (mTORC1), allowing it to phosphorylate its downstream targets, including ribosomal protein S6 kinase (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1). These phosphorylation events initiate a cascade of reactions that culminate in the assembly of the translational machinery and the subsequent synthesis of new proteins. The anabolic potency of leucine is further amplified by its ability to enhance the activity of the insulin/IGF-1 signaling pathway, another key regulator of muscle protein synthesis. Leucine has been shown to increase the phosphorylation of Akt, a serine/threonine kinase that plays a central role in insulin signaling. Akt, in turn, activates mTORC1, further augmenting protein synthesis and promoting muscle growth. In addition to their direct anabolic effects, BCAAs have been implicated in modulating the activity of various transcription factors that regulate gene expression related to muscle growth and metabolism. For instance, BCAAs have been shown to increase the expression of myogenic regulatory factors (MRFs), such as MyoD and Myf5, which are critical for muscle cell differentiation and growth. The anti-catabolic properties of BCAAs stem from their ability to inhibit the ubiquitin-proteasome system (UPS), the primary pathway responsible for protein degradation in muscle

tissue. This intricate system involves the tagging of proteins with ubiquitin molecules, marking them for degradation by the 26S proteasome, a large multi-protein complex that functions as a cellular "garbage disposal."<sup>15,16</sup>

BCAAs have been shown to suppress the expression of key components of the UPS, including the E3 ubiquitin ligases MuRF1 and MAFbx, which are responsible for targeting muscle proteins for degradation. By inhibiting the UPS, BCAAs can prevent excessive protein breakdown and preserve muscle mass in the face of catabolic stressors. The inclusion of eicosapentaenoic acid (EPA) in the nutritional intervention for this patient with cancer cachexia is underpinned by a wealth of evidence supporting its anti-inflammatory and metabolic benefits. EPA, an omega-3 fatty acid, exerts its effects by modulating the eicosanoid pathway, a complex network of lipid mediators that play a crucial role in inflammation, immune function, and cellular signaling. Eicosanoids are derived from arachidonic acid, an omega-6 fatty acid that is converted to pro-inflammatory prostaglandins, leukotrienes, and thromboxanes by the enzymes cyclooxygenase (COX) and lipoxygenase (LOX). EPA, on the other hand, is converted to anti-inflammatory resolvins, protectins, and maresins by these same enzymes, leading to a shift in the eicosanoid profile towards a less inflammatory state. This shift in the balance of eicosanoids has profound implications for the inflammatory milieu in cancer cachexia. By reducing the production of pro-inflammatory mediators, EPA can attenuate the inflammatory cascade that contributes to muscle wasting, anorexia, and metabolic dysregulation. Moreover, the anti-inflammatory resolvins and protectins derived from EPA actively promote the resolution of inflammation and tissue repair, further contributing to the preservation of muscle mass and function.<sup>16,17</sup>

Beyond its anti-inflammatory effects, EPA has been implicated in various metabolic processes relevant to





cancer cachexia. EPA has been shown to improve insulin sensitivity, enhance glucose uptake in muscle tissue, and reduce hepatic gluconeogenesis. These metabolic effects may help to mitigate insulin resistance, a common feature of cachexia, and improve glucose utilization, thereby promoting energy homeostasis and supporting muscle function. Furthermore, EPA has been shown to enhance mitochondrial biogenesis and function, leading to increased oxidative capacity and energy production in muscle cells. This may help to counteract the mitochondrial dysfunction that often accompanies cancer cachexia, contributing to fatigue and impaired exercise tolerance. Recent research has highlighted the intricate relationship between the gut microbiome, the vast community of microorganisms residing in the gastrointestinal tract, and cancer cachexia. The gut microbiota plays a pivotal role in nutrient absorption, metabolism, and immune function, and dysbiosis, an imbalance in the composition of the gut microbiota, has been implicated in the pathogenesis of cachexia.<sup>17,18</sup>

In cancer patients, dysbiosis can lead to increased intestinal permeability, allowing bacterial toxins and pro-inflammatory molecules to enter the bloodstream. This can trigger systemic inflammation, exacerbate muscle wasting, and impair nutrient absorption, further contributing to the cachectic state. Moreover, dysbiosis can alter the metabolism of BCAAs and other amino acids, potentially compromising their anabolic effects. Emerging evidence suggests that modulating the gut microbiome through probiotics, prebiotics, or fecal microbiota transplantation may hold promise as a therapeutic strategy for cancer cachexia. Probiotics, live microorganisms that confer health benefits when consumed in adequate amounts, have been shown to improve gut barrier function, reduce inflammation, and enhance nutrient absorption. Prebiotics, non-digestible fibers that selectively promote the growth of beneficial bacteria in the gut, may also contribute to restoring microbial balance and mitigating the

deleterious effects of dysbiosis. Fecal microbiota transplantation (FMT), the transfer of fecal matter from a healthy donor to a recipient, has emerged as a revolutionary approach for treating various gastrointestinal disorders. While still in its infancy in the context of cancer cachexia, FMT holds the potential to restore a healthy gut microbiome and potentially reverse the metabolic derangements associated with this syndrome.<sup>18,19</sup>

The field of cancer cachexia research is rapidly evolving, with ongoing investigations aimed at elucidating the complex molecular mechanisms underlying this syndrome and developing novel therapeutic interventions. One promising avenue of research involves the exploration of personalized medicine approaches, tailoring nutritional interventions based on individual patient characteristics, such as genetic predisposition, tumor type, and metabolic profile. Another area of active investigation is the development of targeted therapies that specifically address the underlying drivers of cachexia. This includes the development of drugs that inhibit pro-inflammatory cytokines, block catabolic pathways, or enhance anabolic signaling. Furthermore, the integration of nutritional interventions with pharmacologic therapies represents a promising strategy for optimizing the management of cancer cachexia. The potential role of exercise in mitigating cachexia is also being actively explored. Exercise has been shown to stimulate muscle protein synthesis, improve insulin sensitivity, and reduce inflammation, making it a valuable adjunctive therapy for cachectic patients. However, the optimal exercise regimen for cancer patients remains to be determined, and further research is needed to establish safe and effective exercise protocols for this population. The findings of this case report, along with the growing body of evidence supporting the benefits of nutritional interventions in cancer cachexia, have important clinical implications. Healthcare providers should be vigilant in identifying patients at risk for cachexia and



implementing early nutritional interventions to mitigate its deleterious effects. Nutritional assessment, including anthropometric measurements, dietary intake assessment, and laboratory testing, should be routinely performed in cancer patients to identify those who may benefit from nutritional support. The provision of individualized nutritional counseling and education is crucial for empowering patients to make informed decisions about their dietary choices and optimize their nutritional status. The integration of nutritional interventions into the standard of care for cancer patients represents a paradigm shift in the management of this complex disease. By recognizing the critical role of nutrition in supporting physiological function, enhancing treatment tolerance, and improving quality of life, healthcare providers can empower patients to navigate the challenges of cancer and its treatments with greater resilience and hope.<sup>19,20</sup>

#### 4. Conclusion

This case report underscores the importance of a comprehensive and individualized approach to managing cancer cachexia. By harnessing the synergistic potential of high protein intake, BCAAs, EPA, and potentially other emerging therapies, healthcare providers can strive to mitigate the devastating consequences of this syndrome and improve the lives of countless cancer patients.

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