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Eicosapentaenoic Acid Enriched Enteral Nutrition Improves Lean Body Mass in Esophageal, Head and Neck Cancer Patients

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**Title:** Eicosapentaenoic Acid Enriched Enteral Nutrition Improves Lean Body Mass in Esophageal, Head and Neck Cancer Patients

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**Key words:** eicosapentaenoic acid, EPA, esophageal cancer, head and neck cancer, cachexia

## **Abstract**

**OBJECTIVE:** Cachexia is a nutrient deficient condition affecting millions of cancer patients. Cancers of the upper gastrointestinal tract, head and neck are often the most severely affected. Currently, there is no established therapy for cachexia, although several potential anti-cachectic agents are being explored. A meta-analysis was conducted to review the effect of eicosapentaenoic acid (EPA) enriched enteral nutrition on lean body mass (LBM) in esophageal, head and neck cancer patients at risk for progression of cachexia.

**METHODS:** An evidence based review was conducted beginning with a Pubmed database literature search using the terms 'EPA esophageal cancer', 'Eicosapentaenoic acid esophageal cachexia', 'Eicosapentaenoic acid esophageal', 'Eicosapentaenoic acid cachexia head and neck cancer', and 'EPA cachexia head and neck cancer' for human clinical trials. The results were reviewed for relevance and the data from original research was abstracted for amount of EPA enriched formula supplemented, EPA intake, method of intake, LBM measurements, study design, intervention duration, and population characteristics.

**RESULTS:** Three trials were identified that met the criteria and were reviewed. EPA supplementation in enteral nutrition was provided at concentrations ranging between 1.6 g/day and 2.2 g/day for a time span ranging between 3 weeks and 14 weeks. Two randomized clinical trials showed maintenance of > 1.5 kg LBM relative to the control group while a single arm trial showed a gain of 3.2 kg LBM in patients. Differences in results could be attributed to variability in the degree of cachexia, the contents of each enteral nutrition formula, duration of supplementation, and cancer treatments that subjects in each trial were undergoing.

**CONCLUSIONS:** All three trials showed a trend in EPA enriched enteral nutrition improving the loss of LBM in esophageal, head and neck cancer patients at risk for cachexia progression. This type of formula should therefore be considered in treatment of these types of cancers and possibly, in the treatment of other seriously ill patients with cachexia.

## **Introduction**

Cancer cachexia affects approximately 1.5 million patients in the United States and represents 20-30% of cancer patient deaths. Among these patients, the most severely affected are those with upper

gastrointestinal tract, head and neck, or prostate cancer. In these patients, the majority of the weight lost is lean body mass (LBM). Depending on the location of the tumor and its effect on food intake functions, cachexia may progress faster in some patients than in others. Approximately 50% of head and neck cancer patients have some degree of cachexia at death with 20% dying directly from it.<sup>1</sup>

Metabolic changes seen in cancer cachexia cannot be attributed to starvation or reduced food intake alone. The onset of cachexia has been associated with inflammatory cytokine release by some tumors.<sup>1</sup> Biochemical manifestations of cachexia include anemia, hypoalbuminemia, hypoglycemia, hyperlipidemia, and glucose intolerance. Physical manifestations of cachexia include anorexia, skeletal muscle atrophy, accelerated fat loss, and anergy.<sup>2</sup> Cachectic patients may also experience physical, psychological, and social drawbacks.<sup>1</sup>

The severe consequences of cachexia inspire a search for anti-cachectic agents. Among these potential agents is eicosapentaenoic acid (EPA), an omega-3 ( $\omega$ -3) polyunsaturated fatty acid (PUFA) that can replace arachidonic acid ( $\omega$ -6 PUFA) in the cell membrane. Like arachidonic acid, EPA is a substrate for synthesis of inflammatory agents such as prostaglandins and leukotrienes; however, those synthesized from EPA are less potent than those synthesized from arachidonic acid. EPA can therefore mitigate inflammatory responses.<sup>3</sup> Because of cachexia's association with inflammation, there is interest in examining whether or not EPA enriched nutrition formula can counteract the progression of cachexia. This paper reviews clinical trials on EPA enriched nutritional supplementation in esophageal, head and neck cancer patients who have or are at risk for cachexia progression.

## **Methods**

To ensure coverage of all relevant trials, the following words were used in independent searches of the Pubmed database: 'EPA esophageal cancer', 'Eicosapentaenoic acid esophageal cachexia', 'Eicosapentaenoic acid esophageal', 'Eicosapentaenoic acid cachexia head and neck cancer', and 'EPA cachexia head and neck cancer'.

'EPA esophageal cancer' yielded 11 studies, 9 of which were excluded due to a different end point measurement (2), the in vitro nature of the study (2), or studies that did not focus on EPA and cancer patients (5). 'Eicosapentaenoic acid esophageal cachexia' yielded no studies. 'Eicosapentaenoic acid esophageal' yielded 9 results, 6 of which overlapped with the first search and 3 of which were excluded because the study did not focus on EPA and had a different end point measurement. 'Eicosapentaenoic acid cachexia head and neck cancer' yielded 2 studies, one of which was not a clinical trial. 'EPA cachexia head and neck cancer' yielded 2 studies, one of which was not focused on EPA and another of which overlapped with the prior search.

The clinical trials reviewed in this paper were primary studies where changes in LBM were measured as a reflection of improvement in the cachectic condition of patients. Data extracted from these studies included amount of EPA enriched formula intake, method of intake, lean body mass measurements, study design, and population.

## **Results**

The literature search identified three clinical trials that compared changes in LBM before and after EPA enriched formula supplementation in head and neck or esophageal cancer patients. In these studies, most patients had some degree of cachexia and were undergoing surgery or chemoradiotherapy, both of which exacerbate the nutritional status of patients. Ryan et al. and Weed et al. showed a statistically significant improvement in LBM in patients receiving the EPA enriched formula while Fietkau et al. showed a similar trend.

Ryan et al. conducted a randomized controlled trial that examined the effects of enteral nutrition enriched with EPA in the perioperative period on esophageal cancer patients undergoing esophagectomies. 53 patients with resectable esophageal cancer were divided into a control group (n=25) or an experimental group (n=28). Prior to supplementation, 33% of patients in the control arm and 43% of patients in the experimental arm showed weight loss classified as significant or severe. Nutritional supplementation began 5 days pre-op with the experimental group receiving EPA enriched (2.2 g EPA/day) enteral feed and the control group receiving an iso-caloric and iso-nitrogenous standard nutritional feed. Supplementation lasted until 21 days post-op and was administered orally or via a feeding pump. At the end of 21 days post-op, the control group showed a statistically significant loss of -1.9 kg in LBM ( $p=0.03$ ) while the EPA group showed no significant change in LBM ( $p=0.8$ ). A significantly greater number of people in the control group lost >5% body weight compared to the experimental group ( $p=0.03$ ).<sup>3</sup>

Unlike the randomized controlled trial conducted by Ryan et al., Weed et al. conducted a single arm trial investigating the effects of 'protein and energy dense supplementation containing EPA' on head and neck cancer patients undergoing surgery with curative intent. Contents of this supplementation that were not in those of the other two trials included dietary fiber, Vitamin D and K, B-complex vitamins, choline, chloride, calcium, phosphorus, magnesium, iodine, manganese, copper, zinc, iron, selenium, chromium, molybdenum, L-carnitine, and taurine. Patients had lost >12% of their body weight prior to trial entry. Thirty-one patients consumed, in addition to their regular meals, an average of 1.8 containers/day (1.94 g EPA/day pre-op) and 1.5 containers/day (1.62 g EPA/day post-op). Supplementation was ingested orally or via feeding tube from as early as two weeks prior to surgery and throughout the recovery period. At discharge, the patients gained an average of 3.20 kg of LBM, which was a statistically significant difference relative to their trial entry weight ( $p<0.001$ ).<sup>4</sup>

Fietkau et al. carried out a randomized controlled trial that investigated the effects of  $\omega$ -3 PUFA enriched enteral formula (EPA and docosahexaenoic acid (DHA)) on the body composition of 111 patients with inoperable head, neck, and esophageal cancer. Unlike in the other two studies, Supportan, the EPA enriched enteral formula given to the experimental group, is an established enteral formula specifically designed for tumor patients. Supportan contains higher amounts of fat, protein, EPA, DHA and lower carbohydrates relative to the standard nutrition Fresubin energy fibre given to the control group. Enteral nutrition was administered through percutaneous endoscopic gastrostomy and patients were allowed to eat and drink as required. All patients were concurrently undergoing chemoradiotherapy (CRT), which worsens the nutritional status of patients. Patients in the control group (n=56) received Fresubin formula while the experimental group (n=55) received an additional 2.0 g of EPA and 0.85 g of DHA per day through the Supportan formula. At the end of 7 weeks chemoradiotherapy with supplementation, there was no significant difference between the amount of LBM lost between the two groups (0.417). However, with continued enteral supplementation and a follow-up 6 to 7 weeks later, the control group lost 2.67 kg of lean body mass while the experimental group lost 0.96 kg (0.109). While these results did not reach statistical significance (p=0.10), they show a trend in improvement of LBM in patients receiving the  $\omega$ -3 PUFA enriched enteral feed, supporting the results from the above two studies.<sup>5</sup>

While patients in the experimental group of all three trials ingested similar amounts of EPA in enteral formula, patients in Weed et al. showed the most significant improvement, likely due to the additional ions and vitamins provided in their supplementation. Of the two randomized clinical trials, Fietkau et al. showed a less significant result in the EPA group than Ryan et al. perhaps due to the more intense CRT experienced by all the patients. Additionally, there was no mention of starting supplementation prior to the beginning of the CRT treatment in Fietkau et al. as was done in Ryan et al. and Weed et al., whose studies provided supplementation pre-operatively.

**Table 1. Studies in which the effect of EPA enriched enteral nutrition on LBM in esophageal, head or neck cancer cachexic patients was observed.**

Author, Year	Country	Type of Study	N, Gender	Supplementation		Duration	Changes in LBM (kg)		P-value
				Control	Experimental		Control	Experimental	
Ryan et al., 2009	Ireland	Single center, double-blinded, randomized controlled trial	5 F 48 M	Ensure Plus standard nutritional feed  Pre-op: 200 ml BD Post-op: Day 1: 1000 ml Day 2-10: 2000 ml Day 11-21: 1000 ml	ProSure enteral feed with 2.2 g EPA/500 mLs  Pre-op: 200 ml BD Post-op: Day 1: 500 ml ProSure + 500 ml Ensure Plus Day 2-10: 500 ml ProSure + 1500 ml Ensure Plus Day 11-21: 500 ml ProSure + 500 ml Ensure Plus	5 days pre-op 21 days post-op	-1.9 +/- 3.7	No change	Control (Before vs After): p= 0.03* Expt (Before vs After): p=0.8  % of patients who lost >5% body weight (Control vs. Expt): p=0.03*
Weed et al., 2010	U.S.	Single center, open-label, single-arm trial	8 F 23 M	Single-arm trial	1.94 g EPA/day pre-op 1.62 g EPA/day post-op in protein and energy dense oral supplement	23 +/- 2.5 days pre-op 11 +/- 0.85 days post-op	Single-arm trial	+3.20	Before vs After: p<0.001**
Fietkau et al., 2013	Germany	Multicenter, double-blinded, randomized controlled trial	18 F 93 M	1000 mL standard nutrition Fresubin energy fibre	500 mL Supportan formula with 2.0 g EPA + 500 mL of standard nutrition Fresubin energy fibre	Up to 14 weeks	End of Radiotherapy: -2.05 +/- 0.65  Follow-up 6-7 weeks: -2.67 +/- 0.79	End of Radiotherapy: -1.32 +/- 0.59  Follow-up 6-7 weeks: -0.96 +/- 0.66	Control vs. Expt p=0.417  p=0.109

## Discussion

Despite variations in each study, the studies reviewed here support the conclusion that EPA enriched enteral nutrition reduces LBM loss in patients with head, neck, or esophageal cancer. Ryan et al. observed this in patients undergoing esophagectomies. These surgeries often lead to complications such as sepsis and organ dysfunction and patients may take up to 6 months to regain a healthy quality of life.<sup>3</sup> EPA enriched nutrition may therefore be crucial in cancer patients undergoing surgical treatment to maintain body composition during the recovery period. While the other two studies showed maintenance of LBM in the EPA group, Weed et al. observed a significant increase in LBM in cachectic patients, perhaps due to the extra additives in the protein and energy dense supplementation. Fietkau et al. showed a trend in maintenance of LBM with EPA supplementation, but results did not reach statistical significance. This may be because patients were undergoing CRT, which compromises the nutritional status of patients. Additionally, there was no pre-loading period in Fietkau et al. as enteral nutrition was only administered at the beginning of CRT. This is significant because EPA needs a few days to become incorporated into the cell membrane to function. In the other two studies, EPA supplementation began at least 5 days prior to cancer treatment for this purpose.

There were different limitations in each trial. Unlike in Ryan et al., Fietkau et al. did not state whether or not the Fresubin energy fibre provided to the control group was iso-caloric and iso-nitrogenous when compared with the EPA enriched Supportan formula. In Weed et al. and Fietkau et al., patients were also allowed to eat regular meals, and it was not noted whether patients in both groups took in an overall similar amount of calories or not. Without knowing this information, the differences in loss of LBM in Fietkau may not be due solely to the  $\omega$ -3 PUFA in the enteral formula received by the experimental group. In the single arm trial of Weed et al., there was no control group to compare the EPA enriched protein and energy dense formula against; thus the effects of such a formula cannot be definitively concluded. Although these limitations exist, the underlying commonality amongst all three trials point towards EPA enriched enteral nutrition as a potentially effective approach to slow down loss of LBM in head, neck, or esophageal cancer patients.

Treatment of cachexia remains a great challenge.<sup>6</sup> Chemotherapeutic drugs used to treat cancer often lead to cachexia, as they induce vomiting or gut mobility syndromes that reduce food intake. Nutritional support can maintain body weight of cachectic patients, but it cannot maintain LBM.<sup>2</sup> Various approaches for improving body composition have been tested in clinical trials including the appetite stimulant, megestrol acetate, inhibitors of anti-inflammatory pathways, and the hunger hormone, ghrelin. While some of these results seem promising, there is still no definitive approach to treating patients with cachexia.<sup>6</sup> The promise of EPA as a potential anti-cachectic supplement for head, neck, or esophageal cancer patients undergoing surgery or CRT is therefore of great importance. Being able to control cancer cachexia may lead to prolonged patient survival.<sup>2</sup>

Although this review focused on head, neck, and esophageal cancer cases, EPA supplementation in the context of pancreatic cancer and small cell lung carcinoma cases has been explored. While some trials show mixed results, which can be attributed to intervening in different cachexia stages, poor monitoring or compliance, the majority of EPA supplementation studies show positive changes in molecular markers and/or body composition.<sup>7</sup> There has also been specific interest in observing the effect of EPA on preventing cachexia progression in early stage cachectic patients. Kumar et al. conducted a pilot study with 4 g Lovaza (omega-3 acid ethyl esters) administered to 36 cancer patients with early stage cancer cachexia. Results showed improvement in skeletal and visceral protein levels and a decrease in protein degradation.<sup>7</sup> Overall, the studies reviewed here in conjunction with the continuing interest in understanding the molecular effects of EPA make this agent an emerging therapy for treatment of cancer cachexia.

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