

Eicosapentaenoic Acid as Adjuvant for Cachexia in Cancer's Patients

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Abstract

Cachexia is a frequent problem in cancer patients associated with mortality and morbidity since it causes death, reduced therapy effectiveness, as well as decreased quality of life. Cachexia emerges from interactions of several factors, namely metabolic effect of cancer cells, factors released by cancer cells, cytokines release from host cell in response to tumors, and side effects of therapies. Combination of these factors contributes to anorexia, decreased body fat and muscle, and weight loss. Unfortunately, there is no gold standard for treatment of cachexia. Several studies found that eicosapentaenoic acid (EPA) might improve cancer cachexia. It has potential blocking effects on several cachexia underlying factors. It may reverse weight loss, increase lean body mass, and improve the efficacy of therapy and the quality of life. The objective of this literature review is to describe and give basic understanding of EPA as adjuvant for cancer cachexia.

Received:
March 4, 2014

Revised:
June 5, 2014

Accepted:
November 1, 2014

Keywords: Cachexia, cancer, EPA

IJHS. 2015;3(1):1-6

Introduction

Cachexia is one of the most frequent problems found in cancer patients that represents a state of progressive wasting of body fat and muscle which is often accompanied by anorexia.¹ This problem occurs in 50% of cancer patients.²

Cachexia can be the cause of death in cancer patients. Degree of weight loss in cachexia may be used as a prognostic factor; the higher the extent of weight loss, the shorter the patient's survival time.

Cancer patient's condition becomes worse with cachexia because it reduces the patient's tolerance to the toxic effect of therapies. The chemotherapy dosages need to be adjusted in these patients, thus decreasing the treatment effectiveness. Cachexia also has an association with fatigue and poor physical performance, presumably, which then lead to a decrease in the quality of life. Patients become increasingly dependent due to the fact that they have lost their capacity to function normally.^{1,3}

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Several interventions for treating cachexia have shown limited benefits.⁴ The application of hypercaloric feeding has not succeeded in reversing weight loss. Appetite stimulants, such as megestrol acetate, increase appetite but do not result in weight gain.⁵ Raising caloric intake is not sufficient to manage cachexia.

Later studies found eicosapentaenoic acid (EPA) may improve cancer cachexia.⁶ It may block several underlying factors of cachexia. The objective of this review is to describe and provide basic understanding of EPA as adjuvant for cancer cachexia. This review will benefit future research by providing deeper knowledge for effectiveness of EPA in treating cancer cachexia.

Cancer Cachexia

Cancer cachexia is a multi-factorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by using conventional nutritional supports and leads to progressive functional impairment. The pathophysiology of this condition is characterized by a negative protein and energy balance, which is driven by a variable combination of reduced food intake

and abnormal metabolism.⁷ The occurrence of cachexia depends on the cancer type. Cachexia develops more commonly in certain types of cancer (Table 1).¹

Cancer cachexia progresses in three stages, which create a continuum. Precachexia, as the first stage, is characterized by a weight loss of less than 5% and is sometimes accompanied by metabolic and endocrine abnormalities. This stage is followed by Cachexia, which is a stage when the weight loss is more than 5% with systemic inflammation and reduced food intake. The last stage is refractory cachexia, in which there is severe muscle wasting, low performance score, and immune suppression. Prognosis of this stage is poor with expected survival of less than 3 months.⁶ The refractory cachexia can be diagnosed using the following criteria: meet criteria for cachexia; prognosis of less than 3 months; World Health Organization performance status of 3 or 4; unresponsive to anti-cancer therapy; ongoing catabolism at increasing rate; and unsuitable for artificial nutritional support.⁷

A model to assess signs and symptoms of cachexia has been proposed. In this model, four aspects need to be considered: Storage, which assesses the difference between usual to current body weight, velocity of weight loss, weight loss corrected for fluid retention or obesity, and signs of other nutritional deficiency; Intake, which assesses anorexia, satiety, nausea, vomiting, disturbances of taste or smelling, other gastrointestinal symptoms, percentage of normal intake, and dietary diary for 1–2 days; Potential, which assesses tumor [catabolic] activity, C-reactive protein; and Performance, which assesses the performance status, cachexia-related suffering, and the prognosis.⁷

Pathophysiology of Cancer Cachexia

Cachexia emerges from interactions of several factors: cancer cells' metabolic activity, soluble factors that are produced by cancer cells, host's response, and side effects of therapies. This study shows schematic mechanism underlying cachexia (Fig. 1).

One of the most prominent features of cachexia is weight loss. The weight loss results from an energy imbalance. Negative energy balance in the cachexia is a product of increased energy expenditure due to inflammation and decreased energy intake caused by anorexia.

Cancer cells need higher energy to support their excessive proliferation. However, their

metabolic processes are ineffective. These cells need more glucose than the normal cells to generate same amount of adenosine triphosphate (ATP). Cancer cells use glycolysis as the main metabolic activity, a process known as the Warburg effect. It has been suggested that the mutation of Deoxyribonucleic Acid (DNA) that leads to mitochondrial dysfunction prevents cancer cells to use the krebs cycle metabolic pathway. Pyruvate from glycolysis turns into lactate. The accumulated lactate is then transferred to the liver in which 2 mol of lactate is converted to 1 mol of glucose using 6 mol of ATP. This process is called Cori cycle.¹

Table 1 Cancer in which Cachexia Develops³

Malignancy	Patients with Cachexia (%)
Gastric cancer	85
Pancreatic cancer	83
Non-small cell lung cancer	61
Small cell lung cancer	57
Prostate cancer	56
Colon cancer	54
Unfavourable non-Hodgkin's lymphoma	48
Sarcoma	40
Acute non-lymphocytic leukaemia	39
Breast cancer	36
Favourable non-Hodgkin's lymphoma	31

In response to cancer, host cells produce some soluble factors, such as tumor necrosis factor- α (TNF- α) and interleukins (ILs). These cytokines mediate the inflammatory activities. Acute phase response (APR) is a process that normally occurs in inflammatory responses. In APR, liver cells shift production of albumin to C-reactive protein (C-RP). During a normal inflammatory reaction, APR gives beneficial effects. However, in cancer, prolonged APR increases resting energy expenditure (REE), thus accelerates weight loss.^{3,9,10}

Anorexia is a spontaneous, unintended decline in food intake.¹ In this condition, the loss of appetite is caused by the combination of the biochemical and psychological factors. The appetite biochemical regulation depends

on the activity of neuropeptide-Y (NP-Y) and proopiomelanocortin (POMC). These factors present in neurons of hypothalamic arcuate nucleus. Neuropeptide-Y is the main appetite stimulant, while POMC opposes its action. Serotonin and corticotropin releasing factor (CRF), which levels are increased by pro-inflammatory cytokine, depress the activity of NP-Y. These cytokines cause anorexia through their effects in brain nucleus and modulation of neurons appetite regulation.⁵

Psychological factors contribute to anorexia as well. They involve an interplay between the behavioral, emotional, and also the perceptual responses. Examples of behavioral responses are nausea and vomiting, which may cause

patients to avoid eating. Emotional responses, such as fear, depression, and anxiety, which usually are associated with cancer patients, also reduce appetite. Perceptual responses such as beliefs about food may also influence eating habit.¹¹

Energy imbalance is not the only possible cause of cachexia. Cytokines and other factors produced by tumor evoke cachexia by directly stimulating proteins and fat breakdown. The proteolysis inducing factors (PIF) and lipid mobilizing factors (LMF) are soluble factors that are produced by tumor.

Pro-inflammatory cytokines along with the PIF cause skeletal muscle breakdown. They act through the IκB kinase (IKK)

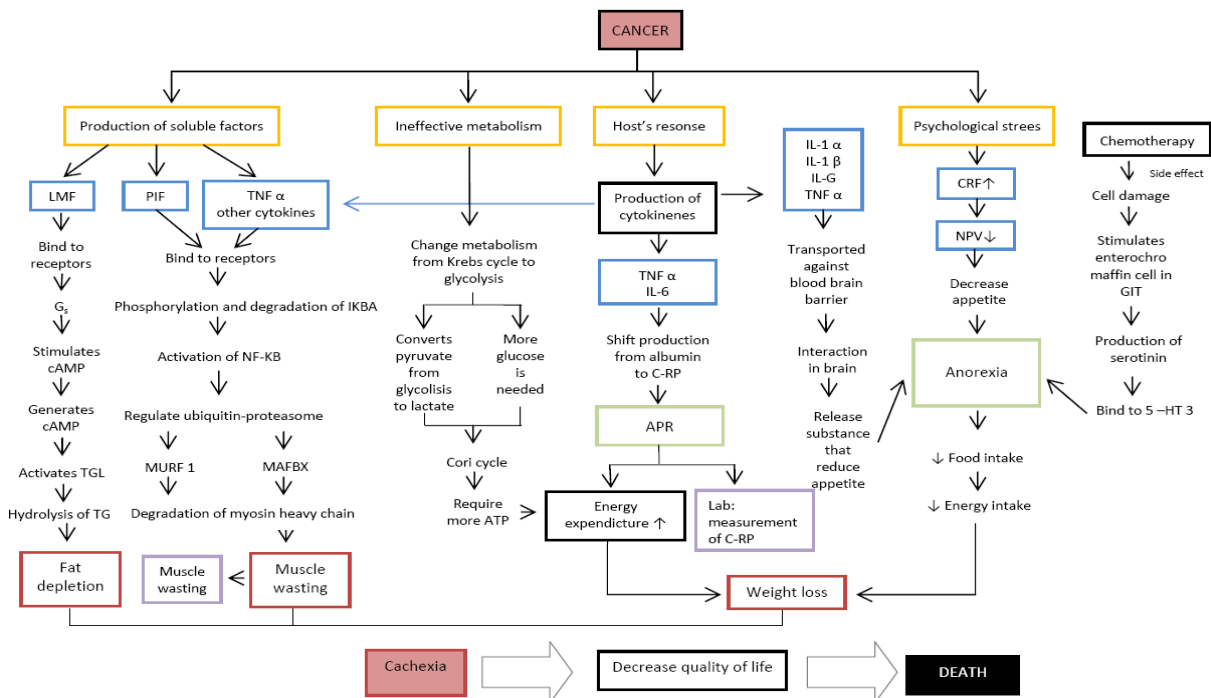


Fig. 1 Cachexia Schematic Mechanism. Abbreviation: AC = adenylate cyclase; APR = acute phase response; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CRF = corticotropin-releasing factor; C-RP = C-reactive protein; DNA = deoxyribonucleic acid; GIT = gastrointestinal track; IκBA = inhibitor kappa-B α; IL = interleukin; LMF = lipid mobilizing factors; MAFBX = muscle atrophy F-box; MURF 1 = muscle RING finger-1; NF-κB = nuclear factor kappa-B; NPY = neuropeptide-Y; proteolysis-inducing factors; TG = triglyceride; TGL = triglyceride lipase; TNF-α = tumor necrosis factor-α; 5-HT 3 = serotonin receptor 3.

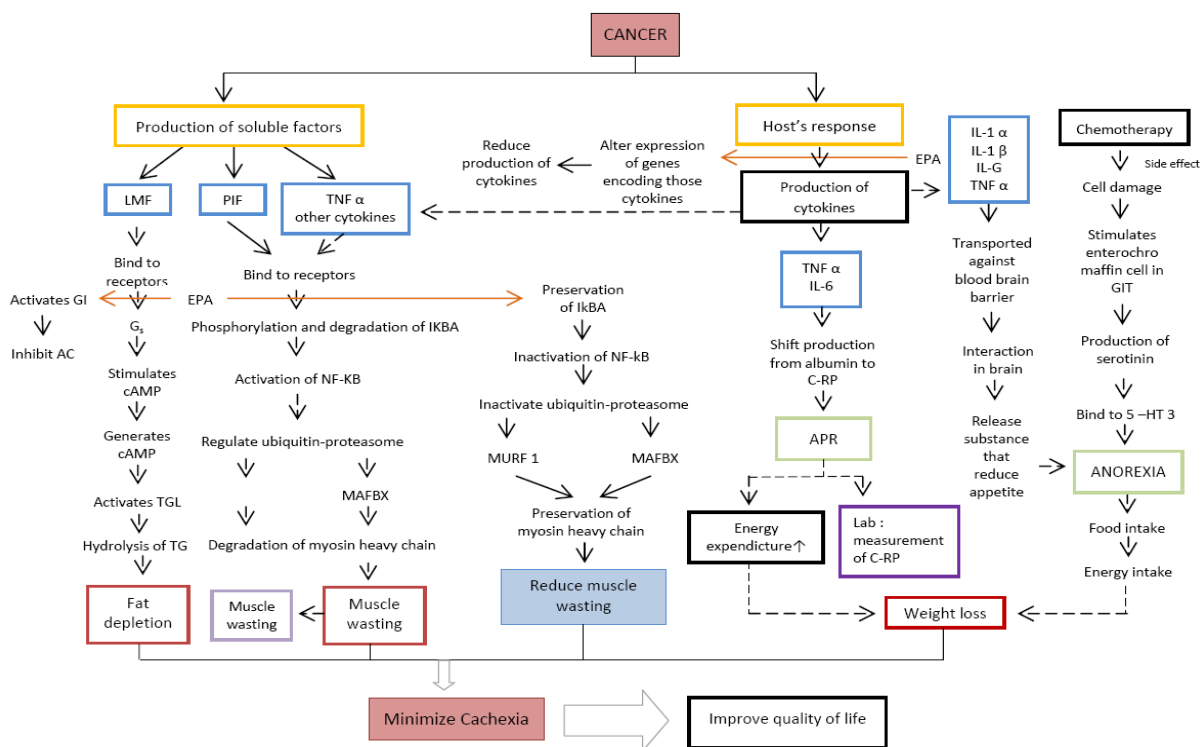


Fig. 2 Schematic Effect of EPA as Adjuvant for Cancer Cachexia. Abbreviation: AC = adenylate cyclase; APR = acute phase response; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CRF = corcotropin-releasing factor; C-RP = C-reactive protein; DNA = deoxyribonucleic acid; GIT = gastrointestinal track; IκBα = inhibitor kappa-B α; IL = interleukin; LMF = lipid mobilizing factors; MAFBX = muscle atrophy F-box; MURF 1 = muscle RING finger-1; NF-κB = nuclear factor kappa-B; NPY = neuropeptide-Y; proteolysis-inducing factors; TG = tiglyceride; TGL = triglyceride lipase; TNF-α = tumor necrosis factor-α; 5-HT 3 = serotonin receptor 3.

complex. This complex phosphorylates and degrades inhibitor kappa-B-alpha (IκBα). The degradation of IκBα permits the activation of nuclear factor kappa-B (NF-κB) to regulate the ubiquitin proteasome activity (Fig. 1). The activation of this pathway produces two muscle-specific ubiquitin ligases, muscle RING finger-1 (MuRF1) and muscle atrophy F-box (MAFBx). These factors induce muscle loss due to proteolysis of myosin heavy chain.²

Lipid mobilizing factors stimulate lipolysis through action of triglyceride lipase. It binds to β3-adrenergic receptor, a G-protein receptor. G-protein receptor consists of three subunits: α, β, and γ. The activity of G-protein depends

on its α subunit. It has Gs and Gi pathways, which activate and inhibit adenylate cyclase, respectively. Adenylate cyclase is an enzyme that catalyzes the formation of cyclic adenosine monophosphate or cAMP from the ATP. Binding of LMF to its receptor activates adenylate cyclase which, in turns, induces the formation of cAMP, causing the phosphorylation and activation of triglyceride lipase. This enzyme then hydrolyzes triglyceride into fatty acids and glycerol. In addition to the mechanism described above, the fat mobilization is also stimulated by TNF-α. Tumor necrosis factor-α induces lipolysis through mitogen activated protein kinase (MEK).¹

Cancer patients are usually treated by using chemotherapy. Chemotherapy triggers adverse effect to normal cells in the body. As a response to the cellular damages causes by chemotherapy, the enterochromaffin cells in the gastrointestinal tract release serotonin. Serotonin binds the serotonin receptors (5-HT₃) in the gastrointestinal tract and the generated impulses are sent to the vomiting center in brain.¹² Vomiting may contribute to cachexia by decreasing the appetite and nutrient intake.¹¹

Eicosapentaenoic Acid

Eicosapentaenoic acid or omega-3 fatty acid is a long chain polyunsaturated fatty acid. Its natural source is fish oil. However, supplementation is now widely available. It has anti-inflammatory activity that has been proven in cell cultures, rodents, and healthy human volunteers. Cell cultures studies have demonstrated that EPA inhibits productions of TNF- α , IL-1b, IL-6 and IL-8 by monocytes, macrophage, and endothelial cells. Hence, fish oil feeding inhibits rodent macrophage production of TNF- α , IL-1b and IL-6 while in human, fish oil supplementation also reduces the production of TNF, or IL-1 or IL-6 by mononuclear cells.¹³

Anti-inflammatory property of EPA is due to its effect in altering the expression of genes encoding the cytokines. It is suggested that EPA modifies activities of transcription factors, such as NF- κ B and/or peroxisome proliferator activated receptor (PPAR)- γ . Eicosapentaenoic acid inhibits phosphorylation of I κ B, which then decreases the activation of NF- κ B and alter the cytokine gene expressions. EPA may also bind to and activate PPAR- γ , which is an anti-inflammatory mediators transcription factor, enhancing its activity.¹³

Anti-inflammatory activity of EPA may have beneficial effects on cancer cachexia. In addition to this anti-inflammatory activity, EPA also has a potential mechanism to block other cachexia underlying factors (Fig. 2).

Proteolysis activity in cachexia can be inhibited by EPA. The decreased production of TNF- α and IL-6 restricts their action on I κ B α . In addition, EPA attenuates the action of PIF on I κ B α . This decreased activity of I κ B α restricts the activation of NF- κ B that will then prohibits the action of ligase. This decreased activity also prevents the proteolysis of muscle fibers protein.¹⁴

Lipid depletion in cachexia can also be blocked by EPA. The LMF action in adipose tissue is attenuated by EPA. Eicosapentaenoic acid increases Gi expression while reducing Gs expression. This increase in Gi inhibits adenylate cyclase and, therefore, inactivates triglyceride lipase and also prevents lipolysis (Fig. 2).¹⁵

Clinical Studies

The beneficial effect of EPA for treatment of cachexia remains inconclusive in many clinical studies. A double blind placebo controlled trial performed by Fearon *et al.*¹⁴ showed no statistically significant benefit of EPA as a treatment for cancer cachexia. However, in that randomized control trial, patients treated with 2 g of EPA gained about 1 kg of body weight compared with those receiving placebo. These patients also showed modest improvement in physical function compared to those receiving placebo. In this trial, instead of 2 g of EPA, some patients were randomly assigned to receive 4 g of EPA. However, patients receiving 4 g of EPA showed no benefit, or rather showed deteriorating effect. It is suggested that the higher EPA doses may create adverse effects that impair gastrointestinal function, thus decreasing food intake.¹⁶ Another trial by Fearon *et al.*¹⁴ suggested that EPA supplementation and identical supplementation without EPA are equally effective in maintaining body weight. However, in post-hoc analysis, only patients receiving EPA supplementation gained body weight and lean tissue mass as was as achieving improvement in quality of life.¹⁴

Experimental studies by Murphy *et al.*¹⁷ suggested that the supplementation of 2.5 g of EPA and DHA significantly increases the efficacy of chemotherapy compared to placebo among patients with lung cancer. Another study in lung cancer patients showed that patients received 2.02 g EPA+ 0.92 DHA had better body weight and fat free mass maintenance compared to control group.¹⁸ Supplementation with fish oil also improved quality of life, performance status, and physical activity compared to placebo.¹⁹

It is concluded that eicosapentaenoic acid shows potential benefits in treatment of cancer cachexia. Further studies are required to determine the role of EPA as an adjuvant for cancer cachexia.

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