

Review Article

## Nutritional Interventions in Cancer Cachexia Prevention and Treatment

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**Academic Editor:** Gerhard Litscher

**Special Issue:** [Cancer Cachexia](#)

*OBM Integrative and Complementary Medicine*  
2020, volume 5, issue 4  
doi:10.21926/obm.icm.2004044

**Received:** September 28, 2020

**Accepted:** November 23, 2020

**Published:** December 7, 2020

### Abstract

Cancer cachexia contributes to 30% of cancer-related deaths. There is currently no treatment or standard of care for cancer cachexia. Many nutritional interventions show promise for the treatment and or prevention of cachexia. Supplementation with omega-3 fatty acids, protein and vitamins either alone or in combination has shown some beneficial effects in the prevention and treatment of cancer cachexia. The mechanisms through which many nutritional interventions work to attenuate cachexia are just beginning to be understood. Therefore, the purpose of this review is to examine several nutritional strategies that have been investigated in the prevention and or treatment of cancer cachexia and provide evidence for the use of additional nutritional interventions to combat cachexia.

### Keywords

Cachexia; nutrition; omega-3 PUFA; protein supplementation; probiotics; fasting; ketogenic; vitamin D



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## **1. Introduction**

Cancer induced cachexia, the unintentional loss of body weight and muscle mass, occurs in approximately 80% of cancer patients and contributes to 30% of cancer-related deaths [1]. While cachexia does not occur with all cancer, it is especially prominent in colorectal, lung, and pancreatic cancers. The cachexia stage correlates with patient morbidity and mortality and the cancer treatments [2, 3]. The loss of skeletal muscle and adipose as well as the metabolic dysfunction and systemic inflammatory environment that occur with cachexia leads to decreased responsiveness to therapies and eventually, poorer prognosis [4-6].

Cachexia is a multifactorial process that includes metabolic dysfunction, systemic inflammation, hypogonadism, and anemia [6, 7]. As there are both tumor derived factors and alterations in the immune system that contribute to muscle and adipose catabolism, it is difficult to understand how to treat this condition best. While the prevention of cachexia has been demonstrated with exercise [8], challenges arise. Most patients are not diagnosed with cachexia until they have significant weight loss, at which point they experience fatigue, and exercise interventions may not be feasible [9]. Hence, treatment strategies become as important as prevention to improve cancer patients' treatment efficacy, quality of life, and survivorship [6]. There is currently no treatment for cachexia, and the target of most treatment is the tumor itself. Therefore, the use of nutritional interventions to prevent and treat cancer cachexia is gaining popularity.

A number of studies conducted in the 1980s attempted to use parenteral nutrition in the treatment and management of cancer cachexia [10, 11]. These studies demonstrated that increased caloric consumption alone was insufficient to attenuate cachexia and did not offer benefits in treating the underlying cancer. Since then, several additional studies utilizing parenteral nutrition have been conducted with similar results. Patients receiving parenteral nutrition experienced more severe adverse events, and there was no improvement in the quality of life [12]. More recent studies using enteral nutrition show more promise and have been shown to improve nutritional status and lower post-operative complications than parenteral nutrition in cancer patients [13]. Additional nutritional interventions have been studied in the context of cancer cachexia that are more targeted toward some of the known underlying mediators of cancer cachexia, including omega-3 supplementation [14], protein supplementation [15], and pro/prebiotics [16, 17]. The purpose of this review is to highlight several nutritional interventions and their potential for the prevention and treatment of cancer cachexia.

## **2. Methods**

A comprehensive search of peer-reviewed journals was completed on a wide range of key terms including but not limited to cachexia, nutrition, omega-3, vitamin D, fasting, time restricted feeding, protein, ketogenic, and probiotics were searched using the NCBI and Google Scholar databases. Only peer reviewed research was used. While there are other nutritional interventions that may aid in the prevention or treatment of cancer cachexia, the topics of omega-3 fatty acids, protein, pre/probiotics, vitamin D, fasting, and the ketogenic diet were selected for this targeted review. Table 1 gives an overview of relevant clinical studies included in this review.

**Table 1.** Review of clinical studies.

Reference	Subjects	Study Design	Intervention	Measurements	Outcomes	Principal Finding
Laviano et al. (2020)	Patients with non-small-cell lung cancer (NSCLC) receiving first-line chemotherapy	1. Targeted medical nutrition (TMN) (Whey protein+n-3PUFA+VitaminD3) 2. Isocaloric comparator	Juice-based TMN drink or milk-based isocaloric comparator drink for 12 weeks, daily.	Adverse events (AES) Vital sign laboratory safety parameters Compliance with nutrition Exercise capacity Survival over 12 months Clinical measures	TMN vs Comparator Smaller number of AES (64 vs 87) Fewer compliance (58.5% vs 73.6%) Exercise capacity favored TMN Smaller patients died (4 vs 10)	TMN containing high dose n3 PUFA, vitamin D and high-quality protein chemotherapy tolerability and has a favorable safety profile.
Del Fibro et al. (2013)	Advanced cancer patient with decreased weight and appetite	1. Fish oil 2. Placebo	Daily high doses of fish oil capsules or placebo (olive oil) for 2 weeks	Appetite Tiredness Nausea Well-being Caloric Intake Nutritional Status Function	No improvement in all of measures in Fish oil group compared to placebo	Fish oil did not influence appetite, tiredness, nausea, well-being, caloric intake, nutritional status, or function after 2 weeks compared with placebo
Murphy et al. (2011)	Patient with non-small cell lung cancer (NSCLC) receiving first-line chemotherapy	1. Fish oil 2. Standard Care	Daily fish oil capsules or standard care for 10 weeks	Weight Skeletal muscle Adipose tissue	Fish oil (69% patients) gained or maintained muscle mass and weight compared with 29% of Standard care	Early intervention with fish oil during chemotherapy resulted in maintenance of weight and muscle mass compared with patients receiving Standard care.

Murphy et al. (2010)	Patients with non-small-cell lung cancer (NSCLC) receiving first-line chemotherapy	1. Sarcopenic patient with NSCLC 2. Non-sarcopenic patient with NSCLC	Chemotherapy 3 cycles over 65 ± 5 day	Muscle mass Plasma phospholipid(n-3) fatty acid	Sarcopenic patients had lower plasma EPA, DHA, and n-3 fatty acid than non-sarcopenic patients.	Plasma (n-3) fatty acids are depleted in cancer patients with sarcopenia, which may accelerate rates of muscle loss
Barber et al. (2004)	Weight-losing patients with pancreatic cancer	Time trial repeated measures with one group	Oral n-3 fatty-acid-enriched with fish oil supplement for 3 weeks	Hepatic synthesis of albumin Fibrinogen Body weight	n-3 fish oil decreased albumin and fibrinogen synthetic rate in the fasting and fed state. Also, patient' weight stabilized	Hepatic protein kinetics were modulated to some degree by an n-3 fatty-acid-enriched fish oil supplement.
Fearon et al. (2003)	Cachectic patients with advanced pancreatic cancer	1. n-3 experiment (E) 2. Control (C)	n-3 fatty acid with antioxidant enriched oral supplement (E) or supplement without n-3 fatty acid with enhanced antioxidants (C) for 8 weeks	Body weight Lean body mass Dietary intake Compliance Plasma phospholipid EPA	Both stopped losing weight and lean body mass. But E patients only have significant correlations between their supplement intake, weight gain and lean body mass.	If taken in sufficient quantity, only the n-3 enriched and protein dense supplement results in net gain of weight, lean tissue, and improved quality of life
Wigmore et al. (2000)	Weight-losing patients with	Time trial repeated measures with one group	Oral supplementation with high-purity EPA	Tolerance/Toxicity Body composition Hematologic and	After EPA, weight was stable.	EPA is well tolerated, may stabilize weight in

	advanced pancreatic cancer		starting at 1g/day to 6g/day for 12 weeks	clinical chemistry Acute-phase protein response Performance status Overall survival		cachectic pancreatic cancer patients
Barber et al. (1999)	Patients with unresectable pancreatic adenocarcinoma, ongoing weight-loss	Time trial repeated measures with one group	Combination of EPA with a conventional oral nutritional supplement per day for 7 weeks	Body composition Dietary intake Resting energy expenditure (REE) Performance status	Weight-gain Increased dietary intake Improved performance status	An EPA-enriched supplement may reverse cachexia in advanced pancreatic cancer
Cereda et al. (2019)	Malnourished advanced cancer patients undergoing chemotherapy	1. Only nutritional counseling (Control) 2. Nutritional counseling with whey protein (WPI)	Whey protein isolate supplementation (WPI) in addition to nutritional counseling for 3 months	Change in phase angle (PhA) Standardized PhA (SPA) Fat-free mass index (FFMI) Body weight Muscle strength CT toxicity	WPI improved PhA, SPA, FFMI, body weight, muscle strength and a reduced risk of CT toxicity	WPI may lead to improved treatment efficacy for malnourished advanced cancer patients
Tozer et al. (2008)	Patients with stage IIIB-IV non-small cell lung cancer	1. Cysteine-rich protein (IMN1207) 2. Casein	Oral administration of the cysteine-rich protein or casein for 6 months	Overall compliance Body weight Survival and Plasma amino acids Hand-grip force	Patients with IMN1207 had an increased body weight, body cell mass, hand-grip	The cysteine-rich protein is sufficient to reverse cancer-related weight loss and the loss of body cell mass which

Storck et al. (2020)	Advanced cancer patient	1. Intervention 2. Control	A leucine-rich supplement in combination with a nutrition and physical exercise program for 12 weeks	Quality of life Performance tests Nutritional status Dietary intake Fatigue Quality of life Clinical course	force, and quality of life  In inter-group, increased handgrip strength and a trend toward an improvement in nutritional status, dietary intake, fatigue, QoL and clinical course	is associated with an improvement of muscle force and certain quality of life parameters. A multimodal therapy combining a leucine-rich supplement with nutritional counselling and exercise is widely accepted by advanced cancer patients, more importantly improved handgrip strength Significantly
Motoorii et al. (2015)	Patients with advanced esophageal cancer receiving neoadjuvant chemotherapy	1. Synbiotics 2. Control	Oral synbiotics (Bifidobacterium, Lactobacillus, and galacto-oligosaccharides) or Biofermin (Streptococcus faecalis) treatment for 6 weeks	The incidence of chemotherapy-related adverse events Changes in fecal microbiota	In synbiotic groups, smaller frequencies of severe lymphopenia, febrile neutropenia and diarrhea. The synbiotic group improved the numbers of beneficial and harmful bacteria	Synbiotics during chemotherapy reduce the occurrence of adverse events of chemotherapy through adjustments to the intestinal microbiota

Osterlund et al. (2007)	Patients with colorectal cancer receiving chemotherapy	1. Lactobacillus GG 2. Fiber	Lactobacillus. rhamnosus GG or fiber-containing nutritional support for 24 weeks	Treatment-related adverse effects	In Lacto-GG showed less grade 3 or 4 diarrhea, abdominal discomfort, hospital care and fewer chemotherapy does reduction due to bowel toxicity	Lactobacillus GG supplementation is well tolerated and reduce the frequency of severe diarrhea and abdominal discomfort due to chemotherapy
Akiba et al. (2018)	Advanced non-small cell lung cancer (NSCLC) patients	1. Vitamin D 2. Placebo	A does of 1,200 IU/day for 12 months	Relapse-free survival (RFS) Overall survival (OS) Serum levels of 25(OH)D Genotyping associated-Vitamin	(Vitamin vs Placebo) Relapse and Death (28% vs 17%) By restricting to subgroup with early-stage 5-year RFS (86% vs 50%) OS (91% vs 48%)	Vitamin D supplementation may improve survival of patients with early-stage lung adenocarcinoma with lower 25D levels, but not advanced stage
Ng et al. (2019)	Patients with advanced metastatic colorectal cancer receiving chemotherapy	1. High-does Vitamin 2. Standard-dose Vitamins	Every chemotherapy cycle (14days). The high group >4000IU/d the standard > 400IU/d until disease progression, intolerance toxicity, or decision to	Progression-free survival (PFS) Tumor objective response rate Grade 3 and adverse events Overall survival (OR) Change in plasma 25D level	High-does vitamin showed higher median PFS and improved supportive hazard ratio	Higher plasma 25-hydroxyvitamin D levels are associated with improved survival in metastatic colorectal cancer

Fearon et al. (1988)	Cachectic cancer patients with severe weight loss	One group 1. Normal diet followed by 2. Ketogenic diet	discontinue treatment  Normal diet on days 1-6 Ketogenic diet on days 7-13	Blood substrates Whole-body protein turnover Insulin concentration Urea and Electrolytes Liver function test	After ketogenic diet, Ketosis blood of glucose, lactate, and pyruvate Body mass No significant alteration in N balance or whole-body protein synthesis, degradation, or turnover rates	Whether the change from glucose to fat-derived energy substrates might reduce tumor growth rates in the long term remains to be determined
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### 3. Omega-3 Polyunsaturated Fatty Acids

There are three types of omega-3 polyunsaturated fatty acids (PUFAs); eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA). EPA and DHA are primarily found in a marine-based source such as fish and krill, while ALA is typically found in plant-based sources such as flax seed. ALA is a precursor to EPA and DHA and is converted albeit not efficiently in humans into EPA and DHA. Omega-3 has known beneficial health effects due to its anti-inflammatory properties and role in cell signaling and membrane fluidity. Omega-3 PUFAs, specifically EPA and DHA, target multiple systems and pathways that are dysregulated during cancer cachexia. There is an imbalance between protein synthesis and degradation during cachexia, leading to unregulated activation of degradation pathways including autophagy and ubiquitin proteasomal degradation, while inhibiting protein synthesis [1, 18]. Concomitantly, there is also a loss of functional energy-producing mitochondria [19]. Much of this imbalance originates with the inflammatory environment (increased IL-6 or TNF- $\alpha$ ) induced by cancer [20]. Omega-3 PUFAs have been shown to be beneficial in preventing lean body mass loss with cancer [20, 21].

Omega-3 PUFAs can modulate pro-inflammatory cytokines production, thereby altering the catabolic stimuli driving cachexia. Independent from its anti-inflammatory function, EPA inhibits cancer-induced protein degradation by inhibiting ATP-dependent proteolytic pathways [22, 23]. EPA has been shown to inhibit protein degradation by suppression of prostaglandin E2 (PGE2) and proteolysis-inducing factors (PIF) in muscle [22, 24-26]. Many cachectic patients develop anabolic resistance with decreased protein synthesis pathways, even when given an anabolic stimulus [16]. By administering omega-3 PUFAs, the blockade of the anabolic response may be reduced and allow for muscle mass maintenance, which has been shown to correlate with cancer survivorship and quality of life, without promoting tumor growth [27, 28].

Fearon et al. demonstrated that cachectic patients have low plasma concentrations of EPA and DHA, so supplementation may prove beneficial [14]. Many studies have shown promising effects of omega-3 PUFA supplementation in advanced cancer patients in helping to stabilize weight [29, 30], attenuate muscle loss [30-33], and increase survival [32, 34]. Wigmore et al. evaluated 26 patients with pancreatic induced cachexia. After increasing the dose over the course of 4 weeks, patients continued with 6g per day of EPA out to 12 weeks. The weight change rate was altered by EPA supplementation from an average loss of 2 kg/month before supplementation to a gain of 0.5 kg/month after four weeks; however, there was no significant change in body composition [33]. A meta-analysis conducted by Colomer et al. found in patients with advanced cancer, a minimum dose of 1.5g per day of omega-3 PUFAs is associated with improved weight, appetite, and quality of life [32]. In a double-blind study utilizing a protein and energy-dense supplement enriched with omega-3 PUFAs and antioxidants, the supplement resulted in a gain of lean mass and improved quality of life if taken in a high enough dose [14].

The mechanisms through which omega-3 PUFAs are able to stabilize weight in cancer cachexia are not fully understood. However, there is evidence that omega-3 PUFAs might aid in suppressing the acute phase protein response, which is elevated in pancreatic cancer cachexia [35], through the modulation of liver protein export [30]. Omega-3 supplementation may also increase whole-body protein anabolism, as demonstrated by Gingras et al. [36]. Skeletal muscle mTOR and p70S6K1 phosphorylation are increased with EPA and DHA supplementation in young and older adults [37, 38]; however, more work is needed to understand if omega-3 PUFA supplementation can override the mTOR suppression and increased protein degradation in patients with cancer cachexia. Taken

together, the results from published data demonstrate potential therapeutic use for omega-3 supplementation in the treatment of cancer cachexia.

#### **4. Protein**

Cancer patients have abnormal anabolic metabolism of amino acids on muscle protein synthesis [15]. Such Metabolic actions can accelerate muscle loss, which leads to an unfavorable prognosis [39]. Thus, it is essential to care for cancer patients by preventing muscle loss. Protein supplementation is demonstrated to be an essential determinant for muscle maintenance in cancer because optimal protein synthesis is required to take high-quality protein. [40]. On top of that, many studies have shown the different benefits of Protein supplementation, such as elimination of toxins, promotion of tissue repair, destruction of pathogens, and prebiotic effects [41]. Therefore, it is possible to assume that providing enough protein with cancer patients would offer crucial precursors for muscle synthesis and a favorable prognosis by suppressing muscle loss.

Tozer et al. conducted a placebo-controlled double-blind trial over a 6-month to investigate whether a cysteine-rich protein may positively or negatively affect the clinical outcome in non-small cell lung cancer patients [42]. The results report that the patients treated with the cysteine-rich protein displayed the increase of weight and the body cell mass. These results may be associated with an increase in muscle force and specific quality-of-life parameters. The authors suggested that cysteine's metabolic function as a biosynthetic factor of proteins and the cellular anti-oxidant affected an oxidative change in the plasma redox conditions and redox-sensitive signaling pathways in the catabolic process [43, 44]. This study shows that specific protein supplementation can be part of an anti-cancer cachexia therapy.

Cereda et al. determined the effects of whey protein isolate (WPI) supplementation besides nutritional therapy in malnourished advanced cancer patients during chemotherapy. This study resulted in improved body composition, muscle strength, body weight, and less chemotherapy toxicity [45]. This could be because whey protein includes plenty of leucine and cysteine, a crucial precursor for glutathione synthesis and muscle protein anabolism [46], which could protect cells by decreasing the oxidative stress conditions involved in chemotherapy and preserving anabolic pathways. Additionally, the result is supported by the fact that whey protein supplementation is rich in various essential amino acids, such as leucine, which could affect the results because it is necessary to maintain muscle protein anabolism [40, 47, 48]. This study emphasizes the efficiency of combination with whey protein and standard nutritional care in malnourished patients undergoing anticancer therapy to interrupt a downward flow.

Several studies have used leucine in the context of cachexia with varying results. Some studies show that leucine supplementation attenuated the loss of lean mass and increased protein synthesis, without increasing tumor mass [49-51], while others show no preservation of lean mass with leucine supplementation [52, 53]. These differences could be related to the timing and dosage of leucine as well as the models used. Despite the differences in the preservation of muscle mass, leucine supplementation has been shown to improve muscle mitochondrial biogenesis and number, and restore tumor-induced losses in energy production [49, 52, 54], which are known to be dysregulated with cancer cachexia and may precede the loss of muscle mass [55]. More work is needed to better understand the utility of leucine and protein supplementation as part of a multimodal approach to treating cachexia.

A recent pilot study published by Laviano et al. was conducted to assess an oral targeted medical nutrition supplement's safety and tolerability containing a combination of n-3 PUFAs, 25-hydroxy-vitamin D3, and high-quality whey protein in cachexia patients with non-small-cell lung cancer during chemotherapy [56]. This study reported that the targeted medical nutrition, including n-3PUFAs, Vitamin D3, and whey protein, positively affected several clinical outcomes measures such as gained weight, metabolic markers, and exercise capacity [57]. Given that IGF-1/mTOR, FOXO3a and IL-6 signaling are associated with muscle wasting in cancer cachexia, the therapeutic intervention, including protein supplement, would change the pathways [58]. This study demonstrates that protein supplement is regarded as a vital constitute, and protein can combine with other nutrition supplements to increase treatment efficiency for cachexia patients with cancer.

A recent multimodal study, combining leucine and physical activity, published by Storck et al. conducted a randomized trial in patients with advanced cancer to determine if the addition of leucine-rich whey protein combined with exercise and a standard nutrition program would affect physical performance and quality of life [58]. This study reported that the multimodal program, including a leucine-rich protein, increased handgrip power significantly. Additionally, physical performance and nutritional status exhibited a positive trend even though not statistically significance [58]. The results present meaningful implications because handgrip strength is a significant prognostic predictor associated with mortality, morbidity, and complications [59]. Considering the complex pathophysiology of cachexia, multimodal interventions should be considered. From this study, we can see the feasibility of the combination of protein and exercise to increase treatment efficiency for cachexia patients.

Based on the studies we found out so far, it is reasonable to assume that protein supplement is necessary for cancer patients, considering a potential role of protein on clinical outcomes and part of a multimodal approach for the cachexia patients. Most of the studies we found were conducted with a small sample size. Plus, there are several limitations in a fair comparison, lack of different cases and experiments. Therefore, scientific evidence of protein supplementation would need to be confirmed by large-scale trials and many cases before recommendations to cancer patients with cachexia.

## **5. Probiotics and Prebiotics**

The gut microbiota has a crucial effect on biological mechanisms in the human body, including nutrient utilization, resistance against infections, maturation of the immune system, and host metabolism [60, 61]. Interestingly, recent studies showed that the balance of gut microbiota is disrupted by tumor cells, cachexia symptoms, and chemotherapy's toxicity [16, 17]. Such a relationship is related to gut permeability, antimicrobial defense, altered intestinal homeostasis, and dysbiosis [62-64]. An unhealthy gut condition would also accelerate the development of a tumor and cancer-related cachexia by fostering harmful bacteria and allowing the translocation of pro-inflammatory bacterial elements [16, 65]. We need to look at the gut microbiota as the potential of nutritional therapy with two sides. First is the direct way of affecting gut microbiota metabolism and improving dysbiosis. Second is the indirect way of maximizing cancer-related treatment efficiency by minimizing the side effects of chemotherapy and alleviating cachexia symptoms.

Bindels et al. conducted an animal experiment to determine if inulin-type fructans (ITF), *Lactobacillus* strains influence cancer cell proliferation [66, 67]. This study reported that Inulin-type

fructans (ITF) reduce cell infiltration markers, systemic inflammation associated with cancer growth. Moreover, ITF increases portal propionate concentration and the activation of free fatty acid receptors, which would inhibit cancer cell proliferation. They concluded that specific *Lactobacillus* strains could decrease cancer cell infiltration into the liver and decrease the inflammation [66]. In a subsequent study, the authors investigated the gut microbiota's role in the therapeutic effects on cancer cachexia using two mouse models of cancer cachexia [17]. They found that synbiotic intervention mitigated some of the dysbiotic patterns and restored antimicrobial proteins' expression controlling the intestinal gut barrier and immune system. Such effects led to reduced cancer cell proliferation, muscle wasting and morbidity, and prolonged survival [17]. These studies showed that synbiotics might improve gut microbiota's function that is impaired by cancer-related factors and so be a crucial therapeutic strategy for cancer cachexia.

Cancer patients struggle with cancer treatment because of gastrointestinal symptoms such as abdominal pain, mucositis, diarrhea, and gut toxicity during chemotherapy [68, 69]. These symptoms would interrupt the digestion of nutrients in patients undergoing chemotherapy and cause muscle loss, which eventually leads to the delay of treatment and even can lead to significant morbidity [68, 70, 71]. Osterlund et al. conducted randomized clinical trials to assess *Lactobacillus*'s efficacy in reducing chemotherapy toxicity [72]. This study found that *Lactobacillus* supplementation reduced grade 3/4 diarrhea (22% vs 37%) and abdominal discomfort in colorectal cancer patients treated with chemotherapy [74]. In line with the previous study, Motoori et al. (2015) demonstrated that the synbiotics, the combination of probiotics and prebiotics, stabilized intestinal microbiota during and after chemotherapy in advanced esophageal cancer patients, and decreased the frequency of side effects of chemotherapy [73]. The author suggests three mechanisms underlying this data. (1) The change of number in harmful and beneficial bacteria. (2) intestinal motility and concentration of short-chain fatty acid. (3) the improvement of epithelial proliferation and the reduction of intestinal apoptosis [73]. These results showed the practical possibility of synbiotics as supplementary nutrition therapy beyond the theoretical potential.

As the importance of gut microbiota has been emphasized, much research on gut microbiota has been going on. Some studies showed the possibility of probiotics and prebiotics or synbiotics; on the contrary, some studies question the efficacy of the method, and even some studies suggest the risk of gut microbiota as a nutritional intervention [74-76]. For synbiotics to be nutritional intervention, further studies should prove the safety and efficacy in cancer patients.

## **6. Vitamin D**

Vitamin D plays a crucial role in bone metabolism and calcium homeostasis (Bouillon and Suda, 2014). In recent years, vitamin D biologic function has been emphasized, including inhibition of cancer cell progression [77]. Vitamin D anti-cancer mechanisms involve inhibition of proliferation, induction of apoptosis and autophagic cell death, and suppressing angiogenesis [78, 79]. Additionally, very recent research confirmed that vitamin D would address immunological infiltrations and cancer stem cell proliferation and affect the tumor microenvironment [80, 81]. With these studies, we can assume that vitamin D has a significant role in tumor suppression.

Many meta-analysis studies support the assumption by demonstrating an inverse association between vitamin D levels and cancer risk. A review paper with meta-analysis [82] investigated the relationship between cancer risk and vitamin D-related genetic variation and circulating 25-

hydroxyvitamin D (25OHD) concentration. This study reported that better cancer outcome has to do with higher vitamin D in cancer patients; similarly, low baseline vitamin D is a clear and strong association with worse cancer survival. Under the analysis, a follow-up study in colorectal cancer patients with stage IV found a significant relationship between higher 25-hydroxyvitamin D level and improved survival among patients undergoing chemotherapy [83]. Therefore, given the association between vitamin D deficiency and poor prognosis, vitamin D's nutritional intervention could benefit selected patients.

Akiba et al. conducted a randomized, double-blind trial comparing vitamin D supplements with placebo in advanced non-small cell lung cancer (NSCLC) patients to examine the relapse-free survival and overall survival [84]. This study reported that vitamin D supplements did not improve either relapse-free survival or overall survival of NSCLC patients, including advanced stages and squamous cell carcinoma or large cell carcinoma. Nevertheless, when the analysis was restricted to the subgroup of patients with early adenocarcinoma with lower 25(OH)D, the relapse-free survival and overall survival significantly are improved in the vitamin D group [84]. Similarly, Ng et al. conducted a double-blind phase 2 randomized clinical trial in patients with advanced or metastatic colorectal cancer to determine whether high-dose vitamin D3 improves outcomes during standard chemotherapy [85]. They found that there is not a significant difference in median progression-free survival between the two groups. However, the supportive Cox proportional hazards analysis showed a significantly better hazard ratio in high-dose vitamins than standard-dose vitamins. These studies show that vitamin's effect can differ depending on the degree and type of cancer and the dose of vitamin [85].

Apart from the studies mentioned above, several research pieces have carried out randomized controlled trials to assess the effect of vitamin D supplementation in cancer patients based on rational evidence [86-88]. Part of the data showed positive results in a specific area, and part of the results did not show significant results. In light of it, there are still apparent limitations and considerations to demonstrate the effect of vitamin D in a clinical area such as effect sizes of vitamins does, small study samples, cancer types, and interaction with other nutritional methods. Therefore, further researches have to be warranted to prove vitamin D as nutritional therapy for cancer patients.

## **7. Fasting**

While it may seem counterintuitive to utilize fasting to help treat a wasting disease driven by increased catabolic metabolism, there is some evidence that fasting could aid in resetting the metabolic program during cancer cachexia thus attenuating further muscle atrophy. There are several different forms of fasting ranging from time-restricted feeding in which individuals feed for a restricted period and fast the remainder of the day and there can be little impact on caloric intake, to fasting that includes longer durations and has decreased caloric intake. Fasting protocols have many health benefits, including improved glucose tolerance and insulin resistance as well as improved symptoms of hyperlipidemia [89-93]. Both caloric restriction and intermittent fasting are associated with reduced cancer incidence [94]. Additionally, fasting is associated with improved cancer treatment efficacy and minimized chemotherapy side effects [95-97].

It has been established that cancer cachexia is associated with altered carbohydrate metabolism, decreased glucose clearance, and lipid dysregulation [98, 99]. While the exact mechanisms of

carbohydrate intolerance are not fully understood, a decrease in peripheral glucose uptake and GLUT4 expression are seen in experimental models of cancer cachexia [100-102]. Additionally, cachexia is associated with mitochondrial dysfunction, dysregulation of the ubiquitin proteasomal system, and alteration in autophagy, contributing to muscle loss and metabolic dysfunction [103-106]. Intermittent fasting has been shown to improve insulin sensitivity and hyperglycemia in both human and animal models [91, 92, 107]. Fasting increases autophagy, which is already upregulated during cachexia; however, autophagy appears unregulated during cachexia. While the exact mechanisms regulating the disruption in metabolic and mitochondrial function and autophagy are not fully understood, a link between these factors and a loss of circadian function may lead to further explanations.

Changes in circadian rhythm and markers of circadian function have been seen in models of cachexia [108-110], and circadian dysfunction is associated with many of the hallmarks of cachexia, including metabolic dysfunction, dysregulation of autophagic flux, and decreased muscle mass. Harfmann et al. demonstrated that post developmental loss of *Bmal1*, a regulator of circadian rhythm, in skeletal muscle leads to decreased fat mass, impaired glucose uptake, and insulin resistance [111]. Similar results are seen by others where a loss of muscle *Bmal1* leads to the upregulation of lipid metabolism and down-regulation of glucose oxidation [112-114]. Additionally, loss of other clock components leads to decreased skeletal muscle mass and function [115]. Autophagy is also regulated by the circadian clock [116]. Fasting alters clock genes' expression in peripheral tissues such as the liver and muscle [117]. Feeding is a strong regulator of the peripheral clocks and can uncouple the peripheral clocks from the central clock, and the use of fasting and feeding can be used to entrain the peripheral clocks [118-120]. It is currently unknown if fasting and feeding can correct the dysregulation of the peripheral clocks during cancer cachexia. More research is needed to understand better the implications of fasting and fasting mimicking diets on lean mass maintenance and attenuation of metabolic dysfunction during cancer cachexia. Careful monitoring of nutritional status should be utilized in these studies as malnutrition could be a risk.

## **8. Ketogenic Diet**

The ketogenic diet is characterized by a low-carbohydrate, high-fat diet that simulates a fasting state without the restriction of calories. When the human body is deprived of carbohydrates, it will naturally shift to producing ketones and fatty acids ( $\beta$  hydroxybutyrate and acetoacetate) as a source of energy [121]. The ketogenic diet has been utilized in pre-clinical and clinical models to target cancer growth [94, 95, 122]. Cancer cells are characterized by the unique phenotype of high aerobic glycolysis rates with lactate production, referred to as the Warburg effect [123]. Thus, cancer cells rely tremendously on glycolysis for ATP to sustain proliferation [124]. The use of the ketogenic diet in cancer patients relies on the fact that cancer cells need glucose for ATP production. However, other tissues in the body, such as the muscle and the brain, can utilize ketone bodies for ATP production and lack of glucose availability for the tumor would prevent further growth [125]. Additionally,  $\beta$ -hydroxybutyrate can suppress the NLRP3 inflammasome, ultimately decreasing IL-1 $\beta$  and IL-18 secretion [126].

Several pre-clinical models have shown anti-cancer effects of the ketogenic diet [122]. Additional studies have shown that the ketogenic diet can be utilized to prevent cancer cachexia [125, 127, 128]. Shukla et al. demonstrated that ketone bodies attenuate both adipocyte and myotube

degradation. Additionally, they demonstrate that inhibition of tumor glucose uptake attenuates muscle and fat loss, suggesting that tumor metabolism plays a critical role in the progression of cancer cachexia [125]. Nakamura et al. utilized a colon cancer model and showed that a ketogenic diet decreased tumor mass and preserved muscle mass [128]. They further demonstrated a reduction in plasma IL-6 with the ketogenic diet in tumor-bearing mice [128]. In a clinical study Fearon et al. established that a ketogenic diet could increase body mass; however, the ketogenic diet was unable to alter the nitrogen balance or rates of protein turnover in cachectic patients [129]. Additional research is needed to further understand the ketogenic diet's role in preventing and treating cancer cachexia.

## **9. Discussion**

The use of nutritional interventions may provide benefits in the prevention and treatment of cancer cachexia. Individually, omega-3 fatty acids, protein, vitamin D, and probiotics can provide some benefits to cachectic patients through varying mechanisms. Additionally, there are a wide array of other nutritional products that may provide therapeutic value to cachectic patients that were not discussed in this review including curcumin, quercetin, resveratrol, pomegranate, and *citrus unshiu* peel to name a few. The research to date primarily uses animal models and small sample sizes. More research is needed in clinical populations to further validate the used of these treatment modalities as well as the feasibility of their use. Additionally, studies need to be done accessing the used of these nutritional interventions both as a prevention for cachexia as well as a treatment for cachexia.

Most of the research to date has focused on single supplement or nutritional approached; however, a multimodal approach to treating cancer cachexia should be considered for greater benefits. Multimodal approaches should include more than just a variety of nutritional strategies. Exercise has been shown to prevent and attenuate cachexia progression in animal studies [8], and when combined with protein supplementation is able to improve grip strength in patients with advanced cancer [58]. Additionally, a phase II clinical trial demonstrated an increased body weight with a 12 week multimodal approach combining exercise, anti-inflammatory medications, nutritional counselling, and EPA supplements in patients with lung and pancreatic cancers [130]. This further demonstrates that a multimodal approach is feasible and may provide the most benefit for patients.

There is currently no standard of care treatment for cancer cachexia, a major contributor to cancer-related deaths [1]. The use of dietary interventions shows promise through a variety of mechanisms. Much of the research to date has focused on the prevention and treatment of the tumor without consideration of the presence or impact of cachexia. While much more research is needed, we have demonstrated the potential for the therapeutic use of omega-3 fatty acids, protein, vitamin D, probiotics, and fasting and fasting mimicking diets in the treatment and prevention of cancer cachexia. The use of nutritional support should be considered as one part of a greater multimodal approach in treating and preventing cancer cachexia.

## **Author Contributions**

Wangkuk Son conducted a literature review and assisted in writing and editing the manuscript. Jason Lin conducted a literature review and assisted in writing and editing the manuscript. Melissa Puppa conducted a literature review and assisted in writing and editing the manuscript.

### **Competing Interests**

The authors have declared that no competing interests exist.

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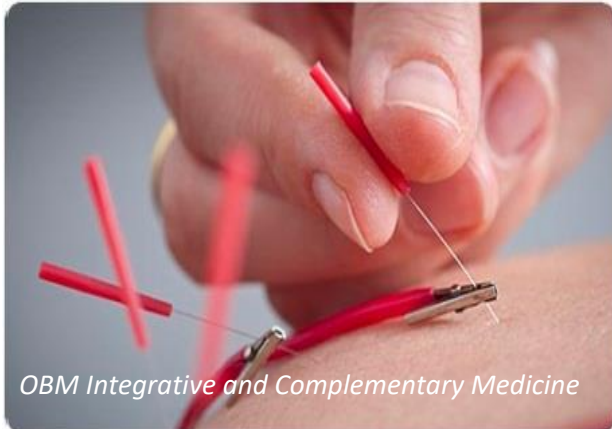
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