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REVIEW ARTICLE

Nutritional Management in Cancer Cachexia

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Abstract

Cancer cachexia is a multifactorial syndrome marked by progressive weight loss, muscle wasting, and systemic inflammation, commonly associated with advanced cancer. Its management poses a significant challenge due to the complex interplay of metabolic alterations, reduced appetite, and inflammation. Addressing the nutritional needs of patients with cachexia is a cornerstone of care, aiming to mitigate weight loss, preserve lean body mass, and enhance quality of life (QOL). Effective nutritional strategies include individualized meal plans enriched with energy-dense and protein-rich foods, alongside the use of specialized nutritional supplements. Pharmacotherapy, such as appetite stimulants, anabolic agents, and anti-inflammatory drugs, plays a crucial role in modulating metabolic dysfunction and supporting nutritional goals. Additionally, physical activity tailored to the patient's abilities has been shown to complement nutritional and pharmacological interventions by promoting muscle retention and functional independence. A multidisciplinary approach that integrates dietary support, pharmacotherapy, and exercise is essential for optimizing outcomes in cancer cachexia management and improving patient well-being.

Keywords: Cancer cachexia; Nutritional management in cancer; Malnutrition in cancer

1 Introduction

Cancer Cachexia is a complex multifactorial syndrome characterized by significant involuntary loss of body weight and skeletal muscle mass, and systemic inflammation leading to severe fatigue, physical debilitation, and decreased survival outcomes in patients with advanced malignancies. This syndrome primarily arises from an imbalance between energy intake and expenditure. Increased basal metabolic rate is frequently observed in cachectic individuals, attributed to tumor-derived factors and a systemic inflammatory response, which drive metabolic inefficiency and elevate energy demands across both tumor and host tissues. Unlike starvation, cachexia involves metabolic alterations that cannot be reversed solely through nutritional support, making it a critical concern in oncology. It contributes to reduced physical function, diminished QOL, and poor treatment outcomes. Consequently, these metabolic alterations exacerbate the negative energy balance and fuel the progressive wasting characteristic of cachexia [1].

Nutritional management is pivotal in addressing the challenges posed by cachexia, focusing on preserving lean body mass, improving energy balance, and mitigating inflammation. Strategies often involve personalized dietary interventions, high-calorie, protein-rich supplements, and pharmacological agents targeting metabolic pathways. Understanding the interplay between cancer metabolism and nutritional therapy is essential for developing comprehensive care plans to improve patient outcomes and overall QOL.

1.1 Definition and Diagnosis of Cancer Cachexia

The Evans et al. criteria, established in 2006, defined cachexia as a ”complex metabolic syndrome associated with underlying illness, marked by muscle loss with or without fat loss”. Weight loss was identified as the primary characteristic of cachexia in adults, with the diagnostic criteria including weight loss as a core criterion and at least three of five additional factors: reduced muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry (including anemia, low serum albumin, and elevated inflammatory markers). In cases where previous weight data is unavailable, a Body Mass Index (BMI) below 20 kg/m^2 was considered as an alternative primary criterion [2]. This diagnostic framework, however, requires specific tools for assessing muscle strength, body composition, and blood biochemistry, which may limit its practicality in everyday clinical settings [3]. Later, in 2009 the SCRINIO protocol (Screening the Nutritional status In Oncologic patients) a structured approach used in oncology to evaluate and address the nutritional risks of cancer patients proposed simpler criteria, using at least 10% weight loss with symptoms like fatigue or reduced appetite, allowing for easier diagnosis of cancer cachexia [4]. The Fearon et al. criteria, established in 2011 further refined cancer cachexia as a multifactorial syndrome involving persistent skeletal muscle loss (with or without fat loss) that does not fully respond to conventional nutritional support and results in progressive functional decline [5]. European Society for Medical Oncology (ESMO) suggests identifying cachexia as a form of disease-related malnutrition according to the Global Leadership Initiative on Malnutrition (GLIM) criteria. This approach emphasizes the role of systemic inflammation as an essential component in diagnosing cachexia.

1.2 Stages of cancer cachexia and evaluation

Fearon et al. introduced a three-stage model for cancer cachexia progression: [5]

1. **Pre-cachexia**, is the initial phase distinguished by mild, unintentional weight loss, reduced appetite, and impaired glucose tolerance emphasizes early intervention
2. **Cachexia**, constitutes the intermediate stage, defined by an involuntary weight reduction of over 5% within six months, the presence of sarcopenia, or unintentional weight loss greater than 2% in individuals with a BMI below 20, requiring multimodal management
3. **Refractory cachexia**, where anticancer therapies are ineffective, with a life expectancy of less than three months.

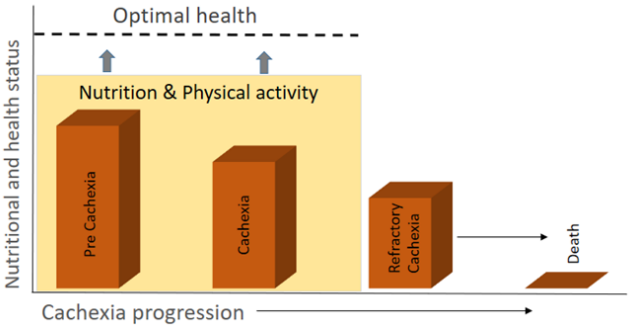

Fig 1. Cancer cachexia progression and health status

The progression of cachexia in cancer patients varies widely and depends on factors such as the severity of the disease, systemic inflammation, reduced food intake, and treatment response[5]. To address this variability, Argilés et al. introduced the Cachexia Score (CASCO) as a quantitative tool for accurately staging cancer-related cachexia. This scoring system evaluates five key dimensions: (1) weight loss and changes in body composition, (2) indicators of inflammation, metabolic disruptions, and immunosuppression, (3) functional performance, (4) anorexia, and (5) QOL. The CASCO scale, which ranges from 0 to 100, categorizes cachexia into four levels: mild (<25), moderate (26–50), severe (51–75), and terminal phase (76–100)[6].

To improve practicality, a simplified version called Mini CASCO (MCASCO) was created, offering a more user-friendly yet reliable method for staging cachexia. MCASCO maintains the validity of the original system while being easier to apply in clinical settings. Both CASCO and MCASCO have been validated and are recognized as effective tools for assessing cachexia across different cancer types, outperforming older classification models.

1.3 Prevalence

Cancer-related cachexia is a leading cause of death in 22–30% of cancer patients and affects up to 74% of individuals with cancer. Its incidence varies by tumor type, being most prevalent in pancreatic and gastric cancers (80–90%) and least common in breast cancer and sarcoma. Gender disparities exist, with males more affected than females, particularly among those over 60 years old, where severe muscle loss occurs in 61% of men versus 31% of women. Malnutrition, present in 15–40% of patients at diagnosis, worsens with treatment, contributing to reduced physical function, poorer QOL, and lower survival rates[7].

1.4 Distinguishing Starvation, Cachexia, and Sarcopenia

Weight loss and wasting can occur due to starvation, cachexia, or sarcopenia, which, though they may appear similar, have distinct underlying causes and biochemical profiles. Starvation-related weight loss is primarily due to caloric deficiency, often leading to adipose tissue loss, with features including stable resting energy expenditure, absence of inflammation, and a reduction in protein breakdown during prolonged deprivation. Unlike other forms, the weight loss in starvation is typically transient and can be reversed with nutritional intervention[8]. In contrast, cachexia involves a progressive loss of skeletal muscle, with a concurrent loss of fat. It is characterized by increased resting energy expenditure, inflammatory markers, and elevated protein breakdown. Cachexia-induced wasting is notably resistant to reversal by standard nutritional support alone[9]. Sarcopenia, on the other hand, is a geriatric syndrome involving the gradual decline of muscle mass and function as part of natural aging[10]. Sarcopenic muscles exhibit a reduction in size and cellularity, predominantly affecting type II fibers, along with increased intramuscular and intermuscular fat infiltration. Additionally, there is a decline in satellite cell quantity and functionality, impairing muscle repair and regeneration[11]. Sarcopenia is largely preventable and, to a significant extent, reversible. Assessing muscle loss purely through body weight measurements can be challenging, especially when excess adipose tissue in obese patients conceals muscle degradation. However, advancements in imaging investigations, particularly through routine CT scans, have improved the ability to analyze body composition changes in cancer patients[8].

1.5 Pathophysiology

Cancer cachexia involves systemic inflammation and negative energy balance, driven by increased energy expenditure and decreased intake, leading to significant weight and muscle loss. This condition is marked by heightened catabolic signaling, mitochondrial dysfunction, and inflammation-driven protein breakdown via autophagy and the ubiquitin-proteasome system (UPS). Elevated inflammatory cytokines and non-inflammatory mediators further suppress anabolic

processes, promoting muscle and fat tissue depletion [1].

There are alterations in multiple organs, including adipose tissue, brain, gastrointestinal tract, cardiac muscle, and immune cells. Tumors that induce cachexia secrete various factors, such as cytokines, parathyroid hormone-related protein (PTHrP), and other mediators, which directly contribute to muscle degradation. These secreted factors also disrupt the normal function of other organs, including the brain, cardiac muscle, gut, and white adipose tissue (WAT), exacerbating the cachexia syndrome. Key mediators implicated in this process include tumor necrosis factor-α (TNF-α), interleukins (IL-1, IL-6, IL-8, IL-10), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). These interactions collectively underscore the systemic nature of cancer cachexia and its multi-organ impact [9].

The hypothalamus controls appetite through two key groups of neurons: neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons that increase hunger and stimulate eating and pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART) neurons that suppress appetite [12]. In cancer cachexia, inflammation disrupts this balance. It activates the POMC/CART neurons (reducing appetite) and inhibits NPY/AgRP neurons (less hunger stimulation). Additionally, inflammatory molecules like IL-1β, IL-6, and TNF-α increase stress hormones and substances like prostaglandins, which suppresses appetite and slows stomach emptying, further worsening eating difficulties [13].

Cancer cachexia significantly disrupts the regulation of Ghrelin, a hormone critical for appetite stimulation and energy balance. Ghrelin levels may be elevated in cachexia as a compensatory response to the profound weight and muscle loss, but its ability to stimulate appetite and anabolic processes is often impaired. This resistance to Ghrelin's effects exacerbates energy imbalance, fueling the progression of Cachexia [14]. This highlights the neuroendocrine dysregulation in cachexia.

Adipose tissue wasting is a key feature of cancer cachexia, driving weight loss and frailty. WAT undergoes browning, adopting brown adipose tissue (BAT)-like properties, which promote lipolysis, thermogenesis via uncoupling protein 1 (UCP1) activation, and energy imbalance. Tumor-derived parathyroid hormone-related protein (PTHrP) exacerbates WAT browning through protein kinase A (PKA) activation and proliferator-activated receptor gamma (PPARγ) suppression via mitogen-activated protein kinase (MAPK) signaling [15]. Adipose tissue fibrosis, characterized by extracellular matrix remodeling and transforming growth factor-beta (TGF-β)/SMAD activation [16], impairs Adipose tissue (AT) function and worsens the prognosis in patients with low subcutaneous adipose tissue (SAT) levels [17]. Inflammation, particularly TNF-α, drives lipolysis, reduces glucose transporter type 4 (GLUT4) -mediated glucose uptake, and contributes to muscle wasting. Early cachexia is marked by WAT lipolysis, while later stages see dominant WAT browning, intensifying metabolic dysfunction [9].

The immune system is central to cancer cachexia, with pro-inflammatory cytokines like TNF-α, IL-1, IL-8, and IL-10 driving muscle wasting, appetite loss, and energy imbalance. TNF-α and Tumor necrosis factor-related weak inducer of apoptosis (TWEAK) activate the UPS, while IL-1 and IL-8 promote muscle atrophy through E3 ligases and the C-X-C motif chemokine receptor 2 (CXCR2)-extracellular signal-regulated kinase 1/2 (ERK1/2) axis [9]. Innate immune cells, such as M2 macrophages, worsen cachexia via signal transducer and activator of transcription 3 (STAT3) signaling, and myeloid-derived suppressor cells (MDSCs) contribute to oxygen consumption and adipose tissue loss. Conversely, adaptive T cells protect against cachexia, with a cluster of differentiation 4 positive (CD4+) regulatory T cells (Tregs) safeguarding muscle and CD8+ T cells mitigating degradation pathways [9].

The gut microbiota, essential for nutrient metabolism and immune function, undergoes significant dysbiosis in cancer cachexia [18]. Tumors and treatments like chemotherapy and radiation disrupt the intestinal epithelial barrier, reducing tight junction proteins like Zonula Occludens-1 (ZO-1) and occludin. This increases gut permeability, allowing bacterial translocation and endotoxemia, which trigger systemic inflammation and exacerbate cachexia [19]. Gut barrier dysfunction, microbial imbalances, and heightened inflammation contribute to disrupted gastrointestinal function, impaired nutrient absorption, and energy imbalance, further aggravating the progression of cachexia in cancer patients.

Cancer cachexia causes cardiac muscle wasting, leading to heart dysfunction. Factors like myostatin, Growth Differentiation Factor 15 (GDF15), and tumor-derived immune factors trigger metabolic changes, including cardiomyocyte atrophy and impaired lipid metabolism [20]. These alterations, along with increased energy expenditure and proteolysis, reduce the heart's oxidative capacity and disrupt mitochondrial function.

Skeletal muscle wasting is a hallmark of cancer cachexia, resulting in significant weight loss and muscle atrophy, impacting patients' QOL. Key pathways involved in muscle degradation include the UPS, autophagy-lysosome pathway (ALP), and calcium-activated degradation [21]. The UPS, especially the activity of E3 ligases like Muscle RING Finger 1 (MuRF1) and Atrogin-1, plays a major role in muscle protein degradation. Autophagy, regulated by the mammalian target of rapamycin (mTOR) and AMP-Activated Protein Kinase (AMPK), is upregulated in cachexia and contributes to muscle proteolysis, with markers like LC3 and BNIP3A elevated in cachectic patients [9]. The calcium-dependent pathway also activates calpain, leading to myofibrillar protein degradation [9]. These pathways collectively drive skeletal muscle atrophy in cancer cachexia, further exacerbating the condition.

1.6 Screening and Assessment

Cancer cachexia plays a critical role in influencing cancer prognosis, yet effective treatment options remain limited. Consequently, early identification of patients at elevated risk of developing cachexia is essential for optimal management [22].

Identifying patients at risk for cachexia presents significant challenges. Cachexia is a type of malnutrition, but few tools are designed specifically to assess its risk, with the CASCO and MCASCO being the only validated tools [6]. ESMO clinical practice guidelines recommend routine nutritional risk screening at regular intervals for all patients receiving anticancer therapy and those with a projected survival of at least 3-6 months. It is recommended to use a validated screening tool, such as the Malnutrition Universal Screening Tool (MUST), Nutrition Risk Screening 2002 (NRS-2002), Short Nutritional Assessment Questionnaire (SNAQ), Malnutrition Screening Tool (MST) or the IAPEN India's Malnutrition Self Screening Tool (IMSST) can also be incorporated into evaluation protocols.

A comprehensive, objective assessment of nutritional and metabolic status for patients at nutritional risk including parameters such as body weight, weight change, body composition, inflammatory markers, nutrient intake, and physical activity is recommended. This evaluation should also account for barriers to maintaining or improving this status, such as nutrition impact symptoms, gastrointestinal dysfunction, chronic pain, and psychosocial distress. Regular re-assessment, typically monthly, is advised to guide and adapt multi-faceted anti-cachexia interventions [22].

In patients with cachexia, prevalent gastrointestinal symptoms include anorexia, early satiety, nausea, bloating, taste changes, xerostomia, dysphagia, and constipation. Additional symptoms impacting nutrition, such as breathlessness and profound fatigue, may also arise. These nutrition-impacting symptoms are frequently observed and are linked to reduced QOL and lower performance status (PS) [23].

1.7 Pharmacological Interventions in Cancer Cachexia

- **Megestrol Acetate (MEGACE) and Medroxyprogesterone (MPA):** Synthetic progestins, MEGACE, and MPA, are widely used for managing cancer cachexia. MEGACE, initially developed as an oral contraceptive, improves appetite, caloric intake, and weight in patients with cancer-related anorexia and cachexia [24]. MPA similarly enhances appetite, stabilizes body weight, and reduces serum levels of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, supporting its anti-cachectic potential [24]. A recent review article by Yu Liang Lim et. al, concluded that megestrol acetate (MA) does not significantly promote weight gain in advanced cancer patients, regardless of dosage (>320 mg/day vs. $\leq$320 mg/day). Moreover, its impact on QOL remains unclear due to limited data. Routine use of MA for cancer-related anorexia/cachexia is not advised, though potential benefits in specific subgroups merit further investigation [25].
- **Ghrelin**: Ghrelin, a 28-amino-acid orexigenic hormone produced in the gut, has shown promise in addressing protein breakdown and weight loss linked to cancer cachexia. This hormone plays a vital role in regulating appetite, maintaining body composition, and balancing energy by stimulating growth hormone secretion and decreasing energy expenditure. Beyond these functions, ghrelin possesses anti-inflammatory, anti-apoptotic, and anxiolytic effects. Short-term use of ghrelin has been found to be safe and well-tolerated, highlighting its potential as a therapeutic option for cancer cachexia. However, more comprehensive research is needed to establish its clinical effectiveness [26].
- **Cannabinoids**: These compounds activate the body's natural cannabinoid receptors and have demonstrated potential in addressing cancer cachexia by enhancing appetite, reducing protein breakdown, and providing anti-inflammatory effects. However, the available evidence regarding their effectiveness in improving appetite, body weight, and QOL in cachexia remains limited and of low reliability [27].
- **Corticosteroids,** known for their strong anti-inflammatory properties, are commonly used in combination with progesterone-based therapies to manage anorexia in patients with cachexia. They have demonstrated benefits in maintaining body weight and enhancing QOL. However, their long-term use is associated with a high incidence of adverse effects, restricting their application primarily to end-of-life care settings [28].
- **Non-steroidal anti-inflammatory drugs (NSAIDs)** are effective as analgesic adjuvants to opioid therapy but have limited efficacy as single agents in improving metabolism or nutritional status in cachexia. Evidence suggests that NSAIDs may contribute to the prevention of cachexia when integrated into multimodal treatment strategies. However, their use in advanced stages of cachexia is associated with adverse events, highlighting the need for cautious and judicious administration to avoid unnecessary complications [28].

1.8 Nutrition Intervention

Malnutrition can significantly worsen clinical outcomes in cancer patients by increasing morbidity and mortality while diminishing treatment effectiveness [29]. Evidence-based nutritional strategies aim to maintain or enhance energy and protein intake, which are crucial for preserving

muscle mass, improving physical performance, and supporting overall treatment outcomes. Implementing appropriate nutritional support not only helps manage symptoms but also contributes to improved tolerance to anticancer therapies and better clinical prognosis. When nutrient intake remains insufficient despite counseling, enteral or parenteral nutrition may be necessary, depending on gastrointestinal function. However, in advanced cancer, the efficacy of nutritional therapy diminishes in the final weeks or days of life[30]. Nutritional interventions are recommended for patients with inadequate food intake, with escalation for those with expected long-term survival or undergoing anticancer therapy. The ESMO and American Society of Clinical Oncology (ASCO) guidelines for cancer cachexia emphasize the prioritization of oral nutrition, with enteral tube feeding recommended for patients with dysphagia. A functional small bowel and a short-term trial of parenteral nutrition (PN) could be offered to select patients, including those with reversible bowel obstruction, short bowel syndrome, or other conditions causing malabsorption[22,31]. Dietary counseling, focusing on protein intake and meal frequency, should be the primary approach, supplemented with oral nutritional supplements (ONSs) as needed. Tube feeding is recommended for patients with head, neck, or upper GI cancers if oral intake is inadequate. For long-term enteral feeding, percutaneous endoscopic gastrostomy (PEG) is preferred over nasogastric tube feeding. PN is considered for patients with severe malnutrition and a good prognosis, though its routine use in chemotherapy patients remains unsupported by evidence[22]. A study evaluating the effects of PN compared to oral feeding (OF) in malnourished advanced cancer patients without intestinal impairment found no substantial benefit of PN. The randomized controlled trial assessed health-related QOL deterioration-free survival, physical functioning, and fatigue, revealing no significant improvements in these parameters with PN. Furthermore, PN was associated with a higher incidence of serious adverse events, particularly infections, compared to OF. These findings underscore the importance of optimizing oral nutrition as the primary approach, reserving PN for specific clinical indications[32].

1.8.1 ***Energy***

The energy requirements of cancer cachexia patients vary widely due to differences in disease stage, metabolic alterations, and treatment effects. General recommendations for these patients focus on preventing further weight loss and meeting altered nutritional needs.

Caloric needs: Energy intake typically needs to exceed approximately 25–30 kcal/kg/day to maintain weight in many cases. Individual needs may vary based on the severity of cachexia and the treatment phase[33].

1.8.2 ***Protein***

Protein requirements for patients with cancer cachexia are higher than those for healthy individuals due to the increased metabolic demands and the need to counteract muscle loss. A positive protein balance is crucial for muscle growth, as the presence of elevated essential amino acids in the bloodstream, sourced from dietary protein, acts as a strong anabolic stimulus[34]. The 2021 ESPEN guidelines recommend a protein intake of over 1.0 g/kg/day for cancer patients, with a target of up to 1.5 g/kg/day with some cases requiring up to 2.0 g/kg/day depending on the severity of cachexia and individual needs, to meet metabolic needs and help prevent muscle loss[35]. Whey protein offers notable benefits due to its high bioavailability, rich branched-chain amino acid (BCAA) content, and cysteine, a precursor for glutathione synthesis. Elevated glutathione levels, crucial for immune modulation, may enhance immune function, though current evidence does not mandate its use as a standard intervention. Whey protein, with its high leucine content and potential to modulate IGF-1 levels, plays a role in supporting musculoskeletal health, which is critical in managing cancer cachexia. Further clinical trials are essential to establish its efficacy as an adjunct in cancer therapy[36]. There is limited evidence on protein quality, including optimal amino acid composition and digestibility, in managing cancer cachexia[37].

1.8.3 ***Leucine***

Leucine, a key branched-chain amino acid (BCAA), plays an essential role in combating muscle wasting associated with cancer cachexia. It supports muscle protein synthesis and inhibits protein breakdown by activating the mTOR signaling pathway and influencing proteasome activity. Research indicates that leucine supplementation can reduce muscle loss, improve protein turnover, and modulate cytokine levels, balancing pro-inflammatory and anti-inflammatory responses. These properties highlight its potential as a therapeutic option for managing muscle wasting in cancer cachexia[37].

1.8.4 ***Glutamine***

A key non-essential amino acid that supports intestinal health and energy metabolism, making it relevant in cancer cachexia. It maintains intestinal mucosal integrity, acts as a precursor for glutathione, and supports metabolic processes. Glutamine supplementation has shown benefits in reducing cachexia severity by preserving body weight, enhancing intestinal structure, and improving glucose metabolism, highlighting its therapeutic potential[37].

1.8.5 ***β-Hydroxy-β-Methylbutyrate (HMB)***

It is a metabolite of the essential amino acid leucine, and has been recognized for its potential role in promoting muscle protein synthesis and reducing protein degradation[38,39],

though its precise mechanisms remain unclear[40]. Commonly consumed as HMB calcium salt, the recommended intake is 3 g/day, with no reported adverse effects, even at higher doses[40]. In cancer cachexia, HMB is hypothesized to counteract muscle wasting by enhancing anabolic processes and mitigating catabolic pathways. Clinical evidence suggests that supplementation with HMB, alongside arginine and glutamine, may improve fat-free mass (FFM)[41], though the independent effects of HMB in cachexia remain underexplored[42]. Notable changes are generally observed after 4–8 weeks of consistent supplementation. While further research is needed to establish definitive clinical recommendations, HMB appears to be a safe and potentially beneficial adjunct in managing cancer cachexia, particularly when combined with a diet rich in leucine-containing proteins to support endogenous HMB production[43].

1.8.6 ***Eicosapentaenoic acid (EPA)***

Cancer cachexia is characterized by inflammation and muscle catabolism driven by cancer-induced pro-inflammatory cytokines (e.g., IL-6, TNF-α) and proteolysis-inducing factor (PIF). EPA has been suggested to counteract these processes by reducing inflammation and restoring metabolic balance[44]. Dietary supplementation with fish oil, rich in n-3 long-chain polyunsaturated fatty acids (lcPUFAs) such as EPA and DHA, has been extensively studied in cancer cachexia. Evidence indicates its potential to preserve skeletal muscle mass, support weight gain, mitigate tumor progression, and enhance nutritional intake[37]. Clinical studies in patients with advanced cancers, such as pancreatic[45] and lung cancer, have reported improvements in body weight, lean body mass (LBM), and muscle function with EPA supplementation[46], though some studies showed no effect on nutritional or functional outcomes[47].

The recommended intake of EPA for cancer cachexia patients is approximately 2 g/day, with studies showing benefits with doses between 1.8 and 2.2 g[45,46]. EPA supplementation is generally safe, with minimal side effects; however, it should be used cautiously in patients with bleeding risks. Significant effects are typically observed after at least 4 weeks of supplementation, with sustained improvements seen over 8–16 weeks[43]. While further research is needed to confirm EPA's role in cancer cachexia, its potential to reduce muscle loss and improve muscle mass makes it a promising adjunct to nutritional therapy.

1.8.7 ***Carnitine***

It is synthesized from lysine and methionine, is predominantly stored in skeletal muscle, and plays a crucial role in enhancing fat oxidation while preserving glycogen[37], which can delay fatigue during prolonged physical activity. While carnitine deficiency is uncommon, it may occur in cancer cachexia due to factors such as reduced dietary intake, impaired synthesis, and increased excretion from chemotherapy. Evidence suggests that carnitine supplementation may help mitigate muscle loss and fatigue in cancer patients, although its efficacy remains inconclusive. The recommended dose for cancer cachexia is around 3 g/day, with effects typically observed after 4 weeks of supplementation[43].

1.8.8 ***Vitamin D***

It plays a complex and multifaceted role in cancer-induced cachexia. While circulating Vitamin D levels are often reduced in tumor-bearing states, muscle expression of the vitamin D receptor (VDR) is paradoxically upregulated. Supplementation with Vitamin D can restore serum levels and enhance VDR expression, but it has limited effects on improving muscle mass or body weight. Studies in vitro demonstrate that Vitamin D can impair muscle cell differentiation, resulting in abnormal fiber formation and reduced myogenic protein expression, likely due to VDR over activation. This suggests that excessive VDR signaling may contribute to muscle wasting in cachexia, warranting cautious consideration of Vitamin D supplementation[48]. Further research highlights contrasting effects of Vitamin D metabolites on muscle health. The inactive precursor, 25-hydroxy Vitamin D (25 Vitamin D), exhibits protective effects by activating Akt signaling, promoting protein synthesis, and maintaining autophagic flux, supporting muscle maintenance. Conversely, the active form, 1,25-dihydroxy Vitamin D (1,25 Vitamin D), induces muscle atrophy by upregulating FoxO3 and atrogenes while blocking autophagy. These adverse effects are mediated by Vitamin D-24-hydroxylase, an enzyme that converts Vitamin D into pro-atrophic metabolites. Silencing this enzyme has been shown to mitigate the harmful effects of 1,25 Vitamin D[49]. These findings underscore the complexity of Vitamin D's role in cancer cachexia and highlight the need for precision in its therapeutic application. A better understanding of the differential effects of Vitamin D metabolites and their regulatory mechanisms is essential to developing effective interventions to counteract muscle wasting in cachexia.

1.8.9 ***Creatine***

Creatine, an organic compound synthesized in the liver, is primarily stored in skeletal muscle as phosphocreatine, where it functions as a rapid energy reserve for adenosine triphosphate (ATP) regeneration during muscle contractions[50]. Research has shown that creatine supplementation helps counteract weight loss and muscle wasting by addressing mitochondrial dysfunction. It improves muscle strength, as evidenced by enhanced grip strength compared to tumor-bearing controls, and inhibits the over activation of catabolic pathways, including the ubiquitin-proteasome and autophagic lysosomal systems. These findings highlight creatine's potential to protect against muscle atrophy in cancer cachexia by supporting cellular energy metabolism and

preserving mitochondrial health[51]. A study investigating the effects of creatine supplementation on muscle wasting in tumor-bearing models showed that creatine supplementation for 21 days protected against body weight loss and muscle atrophy. It reduced plasma levels of TNF-α and IL-6 and minimized changes in spleen morphology. Additionally, creatine supplementation prevented increased levels of Atrogin-1 and MuRF-1, key regulators of muscle atrophy, by attenuating the tumor-induced pro-inflammatory environment. These findings suggest that creatine mitigates muscle wasting in cancer cachexia by modulating inflammation and proteolysis[52].

1.8.10 ***Probiotics***

Probiotics, particularly Lactobacilli, have emerged as a promising therapeutic approach for managing cancer cachexia. Studies have demonstrated that administering *Lactobacillus reuteri* and *Lactobacillus gasseri* reduced markers of muscle atrophy (e.g., Atrogin-1, MuRF1) and systemic inflammation while improving muscle mass and extending lifespan. However, these benefits appear to be species-specific, as *Lactobacillus acidophilus* showed no significant effects[53]. Additionally, attempts to improve gut barrier function and dysbiosis using Faecalibacterium prausnitzii were unsuccessful, highlighting the complexity of gut-microbiota interactions in cachexia. Emerging evidence also suggests that gut fungi, such as Rhyzopus oryzae, could play a role in cachexia management, although further research is needed to confirm safety and efficacy[54].

1.8.11 ***Prebiotics***

Prebiotics, such as galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS), are selectively fermented compounds that support the growth of beneficial gut bacteria like bifidobacteria and lactobacilli, while inhibiting harmful microbes. These compounds enhance gut barrier function, regulate immune responses by interacting with immune cell receptors, and are converted into short-chain fatty acids, which possess anti-inflammatory and anti-carcinogenic effects[55,56]. Recent studies suggest that prebiotics may help alleviate cancer cachexia symptoms by reducing muscle loss, preserving fat mass, and improving gut microbial diversity. However, additional research is necessary to fully determine the therapeutic potential of prebiotics in managing cancer cachexia[37].

1.8.12 ***Fiber***

Emerging evidence highlights the role of gut microbiota dysbiosis and chronic inflammation in muscle loss. Soluble dietary fiber, such as partially hydrolyzed guar gum (PHGG), has shown potential in alleviating muscle wasting by modulating the gut environment. Fiber-rich diets help suppress muscle breakdown by downregulating proteolytic pathways and autophagy markers (e.g., Atrogin-1, MuRF1, LC3, Bnip3). Additionally, dietary fiber promotes beneficial gut bacteria like Bifidobacterium and Akkermansia, strengthens the gut barrier, and reduces systemic inflammation by lowering circulating levels of IL-6 and lipopolysaccharide-binding protein (LBP). These findings suggest that dietary fiber may play a therapeutic role in managing cancer cachexia by mitigating muscle loss and inflammation[57].

1.8.13 ***Astaxanthin (AST)***

It is a naturally occurring marine carotenoid, has demonstrated potential in mitigating skeletal muscle atrophy associated with cancer cachexia. A recent study found that AST, administered at doses of 30, 60, and 120 mg/kg body weight, effectively prevented body weight and muscle loss. This effect was dose-dependent, with notable improvements in muscle fiber size and the expression of myosin heavy chain (MHC). AST treatment significantly reduced IL-6 levels in serum and muscle tissue, though it did not affect TNF-α levels. Additionally, AST countered muscle atrophy by downregulating the muscle-specific E3 ligases MAFBx and MuRF-1. It also improved mitochondrial function by modulating key proteins involved in mitochondrial dynamics and apoptosis. These results suggest that AST, particularly at these doses, could serve as a promising nutritional supplement for managing cancer cachexia[58].

1.8.14 ***Zinc***

Zinc homeostasis is disrupted in cancer cachexia, with excessive zinc accumulation occurring in muscle tissue. Research by Wang G. et al. highlights the role of the ZIP14 transporter as a key factor in this process in metastatic cancer. The upregulation of ZIP14 in muscle cells facilitates zinc influx, impairing muscle differentiation and contributing to atrophy by activating the ubiquitin-proteasome and autophagy pathways. Increased zinc levels also lead to the degradation of myosin heavy chain (MyHC), a protein essential for muscle function. These findings suggest that targeting ZIP14 and modulating zinc uptake could serve as potential therapeutic approaches for managing cachexia in metastatic cancer patients. Furthermore, the study underscores the importance of caution regarding zinc supplementation in these individuals, advocating for careful monitoring and precise therapeutic strategies[59].

The 2021 ESPEN guidelines advise providing vitamins and minerals in amounts close to the recommended daily allowance (RDA) and caution against high-dose micronutrient supplementation unless specific deficiencies are identified[35].

1.9 Physical activity

Engaging in physical exercise is recommended as a strategy to address skeletal muscle loss associated with cachexia by influencing critical disease mechanisms such as protein

metabolism, inflammation, oxidative stress, and mitochondrial dysfunction[60]. Tamayo-Torres et al. highlights the potential of exercise training in alleviating cancer cachexia, as supported by findings from preclinical studies. However, variations in cancer types, exercise regimens, and intervention timing contribute to inconsistent results. In clinical settings, challenges such as diverse exercise protocols, varying cachexia stages, and difficulties with patient recruitment complicate the evaluation of exercise effectiveness. Additionally, the absence of standardized cachexia diagnostic criteria and limited research on advanced-stage patients further impede comprehensive assessment. Future clinical trials aim to shed light on the role of exercise as a supportive therapy for cancer cachexia[60].

1.10 Multidisciplinary approach

Managing cancer cachexia with standard nutritional therapy alone is often insufficient, requiring a strategy that addresses the underlying pathophysiology. According to ESPEN and ESMO guidelines, a multidisciplinary approach that incorporates nutrition, exercise, and pharmacological treatments is recommended, with robust evidence highlighting the importance of nutritional counseling. Combining anti-inflammatory agents, metabolism-boosting therapies, and appetite stimulants with personalized nutritional support and physical activity has been shown to enhance physical function and preserve skeletal muscle mass. These holistic interventions are essential for effectively addressing cancer cachexia[61].

2 Conclusion

Cancer cachexia significantly affects prognosis, requiring early detection and comprehensive management. Detailed evaluations of body composition, metabolic markers, and barriers like symptoms and psychological distress are essential for tailored interventions. Multidisciplinary approaches integrating nutrition, exercise, and pharmacological therapies enhance outcomes. Regular reassessment ensures interventions adapt to evolving patient needs, supporting improved physical function, muscle mass preservation, and overall QOL.

Ethics approval

As a review of published literature that did not involve individual patients, this work did not require IRB approval.

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