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Review Article

Cancer Cachexia: Causes and Therapeutic Strategies

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Abstract

Cancer cachexia affects approximately 80% of cancer patients and is characterized by skeletal muscle wasting and reduced fat mass, resulting in weight loss and short survival time. An in-depth understanding of the mechanisms of cancer cachexia can provide platforms for drug and non-pharmacological management of this condition that claims the life of around 20% of cancer patients. Most of the current work in this field is in the pre-clinical stages. However, such preliminary knowledge is anticipated to help guide the design of large and comprehensive clinical trials to establish the safety and efficacy of therapeutic interventions to treat cachexia.

Keywords: Cachexia, Cancer cachexia, Muscle atrophy, Weight loss.

الهزال السرطاني: الأسباب والاستراتيجيات العلاجية

الخلاصة

يؤثر الهزال السرطاني على ما يقرب من ٨٠٪ من مرضى السرطان ويتميز بهزال العضلات الهيكلية وانخفاض كتلة الدهون مما يؤدي إلى فقدان الوزن وقصر فترة البقاء على قيد الحياة. إن الفهم العميق لآليات الهزال السرطاني يمكن أن يوفر منصات لإدارة هذه الحالة التي تودي بحياة حوالي ٢٠٪ من مرضى السرطان. إن معظم العمل الحالي في هذا المجال في المراحل ما قبل السريرية. ومع ذلك، من المتوقع أن تساعد هذه المعرفة الأولية في توجيه تصميم التجارب السريرية الكبيرة والشاملة لتحديد سلامة وفعالية التدخلات العلاجية لعلاج الهزال السرطاني.

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INTRODUCTION

The word cachexia is derived from the Greek language: “kakos” meaning “bad” and “hexis” referring to “condition” and hence implies “bad condition." Cancer cachexia is characterized by weight loss primarily due to the loss of skeletal muscle mass and an imbalance of protein and energy, which results from a combination of reduced food intake and dysfunctional metabolism [1-3]. Up to 80% of all cancer patients experience cachexia, and at least 20% will lose their lives as a result of respiratory and cardiac failure due to weakened diaphragm and heart muscle [4,5]. Cancer cachexia can impact the patient’s quality of life, elevate the risk of infections, and weaken the efficacy of cancer treatments [6]. Skeletal muscles form 30-40% of the human body mass and regulate several physiological functions, including movement. Maintenance of adequate muscle mass relies on balancing anabolism (protein synthesis) and catabolism (protein degradation) as depicted in Figure 1. The generally accepted definition of cancer cachexia is that “it is a multifactorial syndrome characterized by loss of skeletal muscle mass, with or without loss of adipose tissue, which can only be partially reversed by a nutritional supplement” [3,5,7]. The current diagnostic criteria for cancer cachexia are a) a weight loss of >5% over the past 6 months, b) a body mass index of <20 kg/m² plus a weight loss of >2%, and c) an appendicular skeletal muscle index of both arms and legs, typically obtained using a specialized body composition analysis such as dual-energy X-ray absorptiometry (DEXA) scans, plus a weight loss of >2% [5,7].

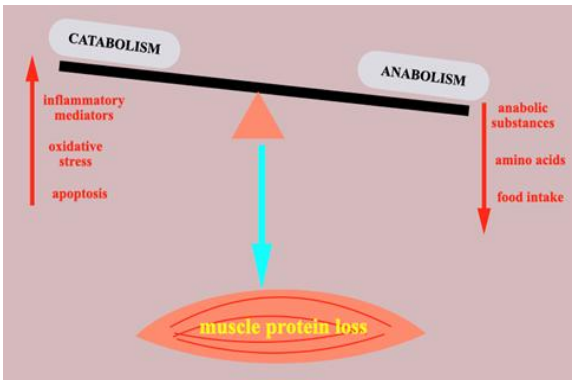

Figure 1: Imbalance between anabolism and catabolism can lead to skeletal muscle atrophy.

Cancer cachexia develops during the late stages of most cancers, although it can be seen early with others such as pancreatic cancer, gastro-esophageal cancer, and lung cancer [4,8]. In pancreatic and gastric cancers, the incidence exceeds 80%, while 50% of patients with prostate, colon, and lung cancers are affected, and around 40% of patients with breast cancer and certain leukemias develop cachexia [9]. The treatment of cancer cachexia continues to be

challenging, and no pharmacological agent has yet achieved a major regulatory approval. Cancer cachexia is believed to entail the involvement of multiple organs, with considerable crosstalk orchestrated between cancer cells and these organs [10]. Muscle atrophy, the loss of skeletal muscle mass, results from cancer-induced activation of the immune system, facilitated by the release of pro-inflammatory cytokines leading to inflammation, increased proteolysis, and reduced protein synthesis [11]. Although cancer cachexia mainly affects skeletal muscles, it can also cause damage to other tissues and organs such as adipose tissue, liver, heart, and bones. Variations between individuals have been observed in the prevalence and severity of cancer cachexia among patients with identical cancer types and stages [12,13]. Also, cancer patients who have mutations that cause the loss of function of the gene that codes for the cell adhesion protein selectin (SELP) are less likely to develop cachexia [14]. A score was created to evaluate cachexia by considering weight loss, anorexia, inflammation, immunosuppression, metabolic changes, and quality of life [15]. The score range is zero to one hundred, with lower scores indicating a mild condition and higher scores pointing to severe and eventually terminal disease. This narrative review will focus on the cause of cancer cachexia and look at possible therapeutic options available to counteract its devastating effect on the patient.

Multi-Organ Involvement in Cancer Cachexia

Systemic inflammation, one of the hallmarks of cancer, is caused by the release of cytokines and other mediators released by tumor cells, immune cells, muscle, or adipose depots [16]. Cancer-derived cytokines such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (INF-γ), interleukin 1-beta (IL-1β), and interleukin-6 (IL-6) are some of the mediators that cause cachexia [17]. The impingement of these inflammatory signals on various parts of the body causes the consequential telltale signs of cancer-associated cachexia (Figure 2).

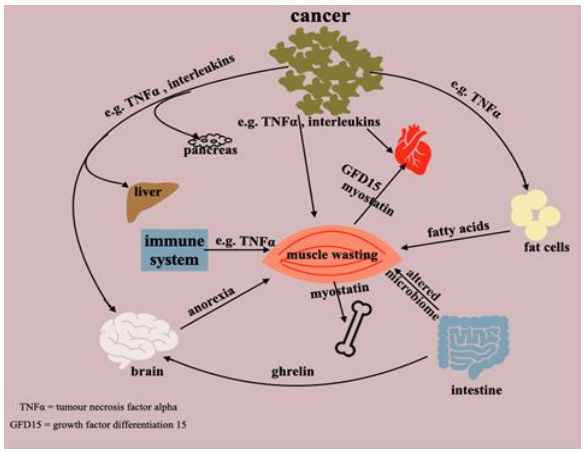

Figure 2: Involvement of various organs and tissues in the cause of skeletal muscle loss and cancer cachexia.

Although skeletal muscle appears to be the main tissue involved in cancer cachexia, many recent studies showed that other tissues and organs such as adipose tissue, gut, heart, liver, pancreas, and brain can directly take part in muscle wasting. Outlines of the link between different organs and cancer cachexia are given below:

Skeletal muscle

Skeletal muscle wasting is a significant feature of cancer cachexia and occurs when protein degradation exceeds protein synthesis, with affected patients showing up to a 33% reduction in quadriceps and up to a 13% loss of skeletal muscle index compared to healthy individuals [11,18,19]. Three major signaling pathways contribute to skeletal muscle loss. 1) ubiquitin-proteasome system (UPS), 2) autophagy/lysosomal pathway (ALP), and 3) Ca^{++}-activated degradation [20,21].

Adipose tissue

It is possible that cancer cachexia is also linked to a loss of adipose tissue because of lipolysis, which breaks down fat cells instead of apoptosis, which destroys them permanently [22]. Cancer patients with cachexia show elevated free fatty acids concentration in their blood, suggesting activated lipolysis [23]. Adipose tissues are of two main types: white adipose tissue (WAT) and brown adipose tissue (BAT), and both types are important for maintaining metabolic homeostasis [24]. Browning of white fat, resulting in what is called beige fat, is a condition in which it acquires BAT characteristics leading to the promotion of a catabolic state, which ultimately induces lipolysis. Thermogenic fat cells (brown and beige) have been activated in cancer patients [25,26]. Thermogenic adipocytes consume calories to help maintain body temperature in response to cold exposure and sympathetic stimulation. However, upregulated thermogenesis via browning of WAT can contribute to energy wasting and weight loss [27].

Immune system

The immune system cells are strongly linked to cancer cachexia through the release of various pro-inflammatory cytokines [3]. The release of TNF-α by immune cells has been directly related to overall muscle wasting through the activation of the ubiquitin-proteasome system (UPS), which is essential for many cellular processes. Higher levels of TNF-α in cancer patients with cachexia result in increased energy expenditure, loss of appetite, and muscle atrophy [28].

Brain

The brain, particularly the hypothalamus, is a key regulator of energy homeostasis, receiving and delivering signals to coordinate food intake and suppress energy expenditure [29]. Inflammatory signals in the hypothalamus activate neurons that regulate hunger and metabolism, including protein and fat breakdown [30]. Cancer cachexia is linked to systemic inflammation, which changes the homeostatic balance in the hypothalamus to turn on neurons that cause loss of appetite, like proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART), and turn

off neurons that cause appetite stimulation, like neuropeptide Y (NPY) and agouti–related protein (AgRP) [31]. The increased levels of pro-inflammatory cytokines in cancer cachexia promote, in turn, higher expression of corticotrophin-releasing factor, a potent anorectic agent, and delay gastric emptying [32]. The parathyroid hormone-related protein has been associated with cancer cachexia by contributing to reduced food intake and facilitating muscle wasting [33,34]. Although loss of appetite is not the only reason for the significant weight loss associated with cancer cachexia, most advanced malignancies exhibit some degree of anorexia [35]. The gut hunger hormone, ghrelin, increases appetite by suppressing anorexigenic neurons and exciting orexigenic ones [2,36]. Moreover, serotonin from the hypothalamus can also modulate both anorexigenic and orexigenic neurons [37].

Gastrointestinal tract

The gut microbiome has an essential role in nutrient usage, the functioning of the immune system, resistance to infections and metabolism. The composition of this microbiome is influenced by tumour cells and previous work has indicated that patients with upper gastrointestinal cancers have a higher prevalence of cachexia than others [38]. The altered gut microbiome can lead to increased permeability of the gut wall to bacteria and bacterial cell wall components allowing easy access to the circulation and causing inflammation. The diarrhea which is often associated with high permeability barriers can result in energy imbalance and absorption irregularities [39]. The diversity of the gut microbiome appears directly influenced by the person's diet and physical activity. Individuals diagnosed with anorexia and elderly patients exhibit a less diverse microbiome composition and diminished muscle function [17]. Colonization of the gastrointestinal tract with microbiome from an obese mouse, but not from a lean mouse, resulted in an increase in body fat in germ-free mice pointing out obesity can be conferred by bacteria [40]. The link between bile acid metabolism, which is known to enhance fat breakdown and regulate signalling molecules, and the gut microbiome may be important in the development of cancer cachexia [41,42].

Heart

Cachexia in cancer plays a role in the wasting of cardiac muscle, which eventually leads to heart dysfunction [11]. A study demonstrated that mice suffering from cancer cachexia exhibited smaller hearts with diminished wall thickness in comparison to healthy control mice [43]. Muscles release molecules like myostatin and growth differentiation factor 15 (GDF15). Immune cells also release other molecules that can start processes that cause cancer cachexia and eventually heart failure [44–46]. Patients often suffer from shortness of breath, decreased exercise tolerance, and fatigue. Heart weight loss is often present when cachexia is present [47]. Higher levels of autophagy and UPS increase oxygen and energy consumption, resulting in a negative energy balance [17,31]. The impact of cancer cachexia on the heart remains largely unexplored, especially its main mechanisms. Animal research has proved significant cardiac atrophy, attributed to inflammation, proteolysis, autophagy, and apoptosis [48].

Bones

The link between bones and skeletal muscles goes beyond the mechanical and structural support. Muscles and bones affect each other by releasing proteins like Indian hedgehog (IHH), which comes from bones and helps muscles grow, and insulin-like growth factor 1 (IGF-1) and fibroblast growth factor 2 (FGF2), which comes from muscles and helps bones form [2]. In sarcopenia, a condition closely linked to cachexia, there is an elevated risk of osteoporosis due to increased expression of myostatin, which is a secreted protein that negatively regulates muscle mass, bone mass, and osteoclast formation [17]. Skeletal muscle weakness is a side effect of cancer metastasis that is partially bone-derived [49]. Pathological levels of transforming growth factor beta (TGF-β) released following bone resorption in metastasis induce profound skeletal muscle weakness due to a reduction in Ca^{++}-induced muscle force.

Liver

Pro-inflammatory cytokines affecting the liver can dysregulate metabolic homeostasis and influence energy production and glycogen storage, which may contribute to cancer-induced weight loss [50,51]. An enlarged liver is often observed in cachectic rodents with tumors and is associated with significant inflammatory markers [52]. The higher levels of protein catabolism and glycolytic flux in patients with cancer lead to elevated plasma levels of lactates and amino acids [53]. These substrates are used in hepatic gluconeogenesis to support tumor growth [54]. The liver contributes to cancer cachexia by increasing energy expenditure and overproducing acute-phase proteins that promote inflammation [1]. Under normal physiological conditions, lactates are produced by skeletal muscle, brain, and red blood cells through anaerobic glycolysis and subsequently released into the bloodstream. The liver converts lactates into glucose through gluconeogenesis, releasing it into the blood or storing it as glycogen based on current conditions. In cancer cells, however, glucose utilization and lactate production are increased because of their aberrant needs. To account for the continuous loss of energy, muscle proteins are broken down, releasing amino acids that can be converted into glucose by the liver [2].

Pancreas

Dysfunction of the pancreas, in addition to its other morbidities, can induce maldigestion and contribute to weight loss [55]. The endocrine secretion of insulin by the pancreas signals the transport of glucose into tissues such as the muscles and suppresses proteolysis [56]. However, the muscle tissue in cancer cachexia becomes insulin-resistant, and protein catabolism ensues. As muscle resistance to insulin occurs prior to

overt weight loss, treatment with insulin-sensitizing agents such as rosiglitazone could partially reverse the insulin resistance and reduce the likelihood of progressive weight loss and cachexia [57,58].

Catabolic/Anabolic Imbalance in Cancer Cachexia

Disturbance of the delicate balance between catabolism and anabolism is a key feature in cancer cachexia, leading to muscle and weight loss [59,60]. The catabolic factors encompass elevated inflammatory cytokines, oxidative stress, and apoptosis, while anabolic drivers can include insufficient food intake, low muscle activity, reduced levels of anabolic hormones, and loss of amino acids (Figures 1 and 3).

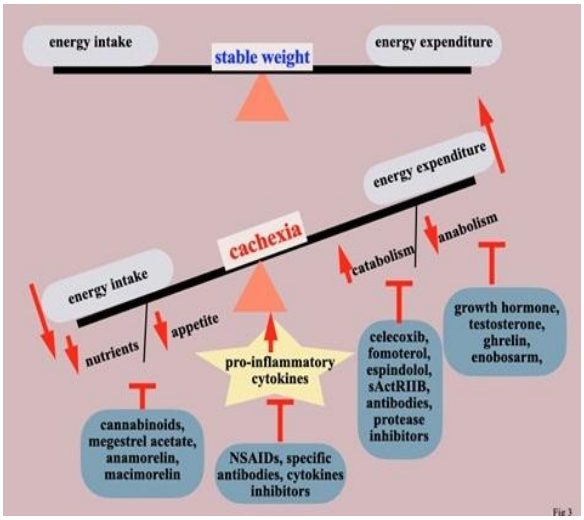

Figure 3: Approaches to restoring the balance between energy intake and energy expenditure.

Catabolic determinants

Inflammatory signals play a major role in orchestrating muscle protein degradation, which takes place through the elevated induction of several potential pathways. These pathways can include 1) the ubiquitin-proteasomal pathway (UPP), 2) the autophagy-lysosomal pathway (ALP), 3) apoptosis, and 4) the calcium-activated pathway. In addition to playing a part in how cancer starts and spreads, inflammation may also cause cachexia and be the main cause of muscle loss because it speeds up the breakdown of muscle proteins and slows down the production of new ones [61]. Skeletal muscle atrophy is associated with decreased levels of myosin and troponin, which are essential for sarcomere structure [62]. Pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 that are produced by either the tumor or by the host in response to the tumor have been shown to activate NF-κB, which inhibits the synthesis of muscle-specific transcription factors such as MyoD, thereby inhibiting differentiation [60,63,64]. The pro-inflammatory cytokines also upregulate UPP to facilitate muscle breakdown and inhibit protein synthesis [65,66]. Exosomes that cancer cells release may also be involved in cachexia, according to recent studies [67]. These are nanometer-sized vesicles that take part in the transfer of materials (such as proteins, lipids, and nucleic acids, which could be translated into information) between cancer cells and their microenvironment. Small molecules called miR-21 and miR-26a, which are found in exosomes, may help control muscle loss in cancer patients who are developing cachexia [67]. In addition to the cytokines, myostatin and activin are also involved in the muscle atrophying process [68]. The activity of skeletal muscles continuously releases oxidants such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), which under normal circumstances are kept in balance with antioxidant mechanisms [69]. A sustained increase in ROS may cause tissue injury due to oxidative damage [70]. A disturbed balance between oxidants and antioxidants can lead to the loss of normal redox equilibrium, a condition called oxidative stress. When the production of ROS and RNS surpasses the cellular antioxidant levels, oxidative stress will ensue. Skeletal muscle damage associated with cancer cachexia has exhibited protein oxidation, suggesting the involvement of oxidative stress with elevated ROS production in the mitochondria [69]. Reactive oxygen species upregulate the expression of key components of UPS and increase their activity, resulting in a higher level of muscle protein degradation. The presence of cancer, and in particular its secreted TNF-α, can stimulate the production of ROS in the mitochondria. Moreover, the excessive accumulation of mitochondrial uncoupling proteins in cancer cachexia can impair the membrane potential of these organelles, leading to increased production of mitochondrial ROS. The activation of ROS and RNS triggers NF-κB to participate in proteolysis [69,71]. Additionally, elevated levels of ROS/RNS can oxidize specific cysteine residues in proteins, which eventually leads to their ultimate degradation [72]. In addition to the protein degradative pathways mentioned above, apoptosis is also an important route. Apoptosis was found to occur in skeletal muscle undergoing cancer cachexia and was detected in the skeletal muscle of the gastrointestinal tract of cancer patients [73,74]. Gastrointestinal tract cancer patients exhibited a three-fold increase in muscle DNA fragmentation compared to controls and were associated with a four-fold increase in poly (ADP-ribose) polymerase cleavage, a useful hallmark of apoptosis [73]. These results point to the presence of muscle apoptosis and confirm that it plays a part in cancer cachexia. Activated caspase 8, caspase 9, and phosphorylated p53 proteins were found to be higher in cancer cachexia compared to control, indicating that apoptosis may be involved in cancer cachexia related to skeletal muscle loss [74]. Impaired muscle protein synthesis, rather than the straightforward breakdown of existing proteins, also plays a part in overall muscle wasting. In this regard, TNF-α activates the transcription factor NF-κB, which inhibits the synthesis of the muscle-specific transcription factor MyoD (myoblast determination protein-regulator of the terminal differentiation of muscle cells), thereby inhibiting differentiation. TNF-α is also partially responsible for increasing the levels of myostatin (an endogenous negative regulator of muscle growth) [68].

Anabolic determinants

Inflammation in cancer cachexia initiates anorexic pathways that restrict the intake of nutrients. Amino acids are required for muscle proteins, and their reduced availability is a major contributor to the loss of skeletal muscles in cancer patients with cachexia. The anorexic response also lowers the sensitivity to insulin, which is known to be a potent stimulator of muscle protein synthesis [75]. Figure 4 shows a schematic of the protein mTOR, which is a key player in the anabolic response. It receives signals from insulin and amino acids to turn on the proteins that come after it. This signaling pathway is inhibited in cancer cachexia.

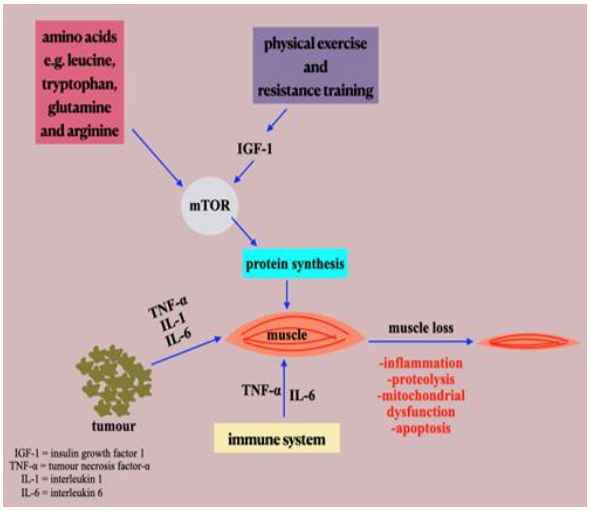

Figure 4: The central role of mTOR in orchestrating the body's anabolic response.

Unlike the behavior of subjects starved of food, patients with cancer cachexia display decreased appetite and show disinterest in feeding even with the higher catabolism possibly needed to compensate for the lack of amino acids [76]. Multiple factors contribute to appetite changes in cachexia, notably depression and anxiety associated with the ongoing malignancy. Furthermore, side effects such as nausea, vomiting, and gastrointestinal inflammation caused by any existing cancer treatments can also contribute to anorexia [77]. Tumor-released substances such as lactic acid, in addition to the inflammatory cytokines resulting from cancer-host interactions, can also cause appetite suppression through direct action on the hypothalamus [78]. Active nutrients affect different pathways, which may be deregulated in cancer cachexia [79]. Preventing any deficiencies in rate-limiting nutrients will help to maintain the metabolic homeostasis. Nutrient support aims at counteracting the negative energy balance and the net protein loss without encouraging tumor growth or negatively influencing cancer therapy. Specific nutrients should be considered to establish a positive protein balance between mitigating catabolic and stimulating anabolic signals. Adequate and balanced nutrients are essential to create an anabolic trigger that will lead to an increase in muscle mass and its maintenance. Cancer cachexia is associated with insulin resistance, and that represents a significant metabolic disturbance [56]. Chronic exposure to pro-inflammatory cytokines TNF-α and IL-6 has been reported to induce insulin resistance by directly impairing insulin signaling while simultaneously fueling tumor growth [80]. The impairment of insulin signaling in muscles disrupts pathways like PI3K/AKT/mTOR that are essential for protein synthesis [56]. Insulin-like growth factor 1 (IGF-1) is one of the main positive regulators of muscle growth [81]. This growth factor, IGF-1, blocks myostatin signalling and prevents TNF-α-mediated apoptosis [81].

Management of Cancer Cachexia

The management of cancer cachexia includes the use of non-pharmacological interventions such as nutritional support and physical exercise as well as the use of medicines (Figure 5). The best way to manage cancer cachexia is to cure the cancer, although this remains an infrequently achieved goal among advanced malignancies [82].

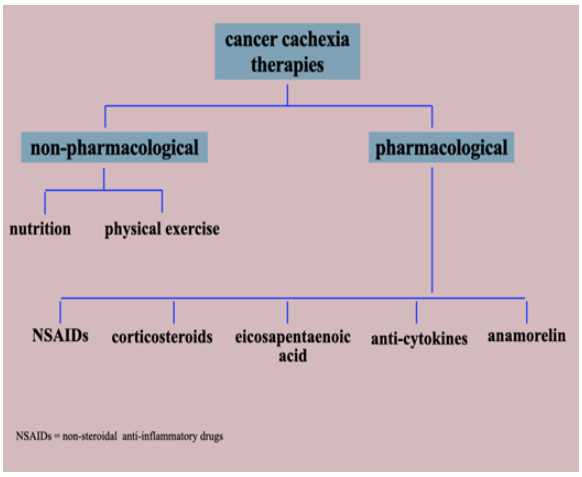

Figure 5: Therapies for cancer cachexia.

The management goal should be to reverse the loss of body weight and muscle mass and to include assessment and repeated monitoring, nutritional support, physical exercise, and pharmacological interventions when indicated to counteract cachexia as well as minimize its complications.

Nutritional support

Various nutrients have been employed to regulate and normalize metabolic processes in cachectic cancer patients.

Amino acids and related compounds

Branched-chain amino acids (BCAAs) are thought to exert a therapeutic effect being integral components of skeletal muscle proteins, and they play a critical role in protein synthesis [83]. BCAAs may decrease proteolysis and increase protein synthesis primarily through the activation of the mTOR pathway and the modulation of inflammation through glutamine production [84,85]. Leucine is one of the BCAAs with a potent stimulant action in muscle protein synthesis [84]. An amino acid-related compound called β-hydroxy-β-methyl butyrate (HMB), which is synthesized in the body through metabolism of L-leucine, is thought to suppress protein degradation [86]. Glutamine is one of the precursors of glutathione,

which is a major antioxidant and a vital part of host defenses [87]. Marked depletion of glutamine is observed in some cancer patients and is thus thought useful for the treatment of cancer cachexia [88]. Glycine has demonstrated efficacy as an anti-inflammatory amino acid with immunomodulatory properties [89]. Dietary glycine was reported to inhibit the growth of certain cancers such as liver cancer and melanoma [90,91]. However, more research is needed to establish the effect of glycine on cancer cachexia. Arginine is another amino acid involved in a number of biochemical processes, including protein synthesis and cell growth. It is also a precursor in the biosynthesis of nitric oxide, a cellular messenger that stimulates the release of certain hormones such as insulin and growth hormone [92]. Arginine may also enhance natural killer cell activity to inhibit cancer growth, and therefore supplementation with arginine could be useful to the cachectic cancer patient [93]. Multiple investigations indicate that tryptophan plays a crucial role in protein synthesis and shows specific anti-inflammatory properties. It has been identified as a contributor to the activation of the mTOR pathway via IGF-1 [94].

Dietary fat

Fat is an important source of energy and functions as a structural component of cell membranes, transports fat-soluble vitamins, plays an important role in signal transduction, and acts as a precursor for inflammatory mediators [95]. Ketogenic diets are high-fat, low-carbohydrate diets designed to increase the blood concentration of free fatty acids and ketone bodies, thus providing alternative sources of energy to glucose [96]. As cancer cells rely mostly on glucose as a substrate for anaerobic energy production, ketogenic diets aim to reduce energy sources for the cancer cell while providing free fatty acids and ketone bodies as energy sources for the muscle [97]. Long-chain polyunsaturated fatty acids influence diverse physiological processes affecting normal health and chronic diseases [98]. Diet supplementation with fish oil has been investigated as a way to preserve skeletal muscle mass in cancer cachexia [99]. Conjugated linoleic acids, which are isomers of linoleic acid found mostly in red meat and dairy products, are marketed as weight-loss supplements to reduce body fat and improve lean muscle growth [100].

Physical exercise

Physical activity increases insulin sensitivity and the activity of antioxidants as well as improves protein synthesis, and all of these outcomes could be useful in the treatment of cancer cachexia [101]. Exercise may also suppress inflammatory response and improve immune function, which could have a beneficial influence on cancer therapy and the cachexia associated with the malignancy [102]. There is evidence that endurance training (ET—where repeated exercise movements are done against low resistance for an extended time) counteracts the fatigue associated with cancer [103], while resistance training (RT—where a lower number of exercise repetitions are performed against higher resistance) attenuates muscle wasting [101]. Endurance training has been documented to increase anti-inflammatory markers such as IL-8 and IL-15 and lower markers for oxidative stress [104,105]. Resistance training, on the other hand, has been observed to prevent muscle atrophy and reduce inflammation by decreasing the expression of TNF-α and IL-6 [106]. In a randomized CT on pancreatic cancer patients, RT improved body weight by 3.2% and muscle strength by 30% [107]. ET has also demonstrated in a similar way that it can also significantly improve muscle strength [108].

Pharmacologic interventions

Due to the complex nature of cancer cachexia and the involvement of multiple factors such as anorexia, muscle loss, and metabolic alterations, comprehensive treatment should be sought. Such a therapy schedule should not only be based on drug treatment but also include nutritional supplementation and physical exercise as outlined before. A range of pharmacological treatments has been studied, and a summary of relevant options that have yielded some promising results is shown in Table 1.

Table 1: Pharmacologic interventions in cancer cachexia

Compound	Mechanism of action	Outcome	Reference
Corticosteroids e.g., prednisolone, dexamethasone, and methylprednisolone	Unknown (speculated to be euphoria, inhibition of prostaglandin metabolism and IL-1)	Improve symptoms of anorexia and fatigue	[109]
Progestogens e.g., megestrol	Orexigenic appetite stimulant	Increase appetite and body weight	[110]
NSAIDs	block cyclooxygenase pathways and inhibit prostaglandin synthesis	Reduce inflammation and pain	[111]
Olanzapine	Acts on multiple receptors including adrenaline and dopamine. Serotonin and histamine	Improve weight gain and appetite	[112]
Thalidomide	Inhibits TNF-α synthesis	Reduce inflammation and improve appetite	[113]
Androgens e.g., enobosarm	Androgen receptor modulation	Reduce fatigue and increase muscle mass	[114]
Beta-blockers e.g., espindolol	non-selective beta-blockade	Reversal of weight loss improvement in fat mass	[115]
Targeting pro-inflammatory cytokines e.g. myostatin	inhibition of pro-inflammatory cytokines.	Reduced inflammation and improved weight gain	[116]
Anti-GDF-15 agents e.g., ponsegromab	Reducing circulating levels of GDF-15	Improve weight gain	[117]
Ghrelin mimetics e.g., anamorelin	Ghrelin-receptor agonist	Increases appetite, weight and muscle mass	[118]

NSAIDs=non-steroidal anti-inflammatory drugs, TNF-α=tumour necrosis factor alpha, GDF-15=growth differentiation factor-15.

Conclusions

This overview outlines our current knowledge of cancer cachexia and its management. Several cytokines, neuropeptides, and neurotransmitters, as well as tumor-derived factors, are involved in the pathophysiology of cancer cachexia, with skeletal muscle atrophy being one of its main features. Due to the multifactorial nature of cancer cachexia, its management is usually personalized and includes pharmacologic and non-pharmacologic modalities based on the underlying mechanisms observed. Several drugs have shown promising preliminary results but require further extended clinical trials to establish their efficacy.

Conflict of interests

The author declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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