Saudi Journal of Medicine and Public Health

https://saudijmph.com/index.php/pub

https://doi.org/10.64483/202522732

Anorexia and Cachexia: Multidisciplinary Assessment, Diagnosis, Prevention, and Management Across Nursing, Clinical Nutrition, Physical Therapy, Diagnostic Radiology, Public Health, and Epidemiology

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Abstract

Background: Cachexia is a multifactorial metabolic syndrome associated with chronic diseases, particularly advanced malignancies, chronic obstructive pulmonary disease, heart failure, chronic kidney disease, and chronic infections. It is characterized by progressive skeletal muscle wasting, adipose tissue loss, systemic inflammation, and metabolic dysregulation that cannot be fully reversed by conventional nutritional support. When accompanied by severe appetite loss, it manifests as anorexia-cachexia syndrome, resulting in substantial functional decline and increased mortality.

Aim: This review aimed to provide a comprehensive overview of the etiology, epidemiology, pathophysiology, clinical assessment, diagnostic evaluation, prevention, and multidisciplinary management of anorexia and cachexia while highlighting evidence-based strategies that improve patient outcomes across multiple healthcare disciplines.

Methods: A narrative educational review was conducted by synthesizing current evidence, international clinical guidelines, and published literature regarding the mechanisms, diagnosis, nutritional assessment, functional evaluation, and therapeutic management of cachexia in patients with chronic diseases.

Results: Cachexia develops through complex interactions among chronic inflammation, neuroendocrine dysfunction, metabolic abnormalities, and impaired protein synthesis, resulting in progressive muscle wasting and functional deterioration. Early diagnosis requires comprehensive clinical, nutritional, anthropometric, laboratory, and functional assessments. Management is most effective when multidisciplinary, integrating nutritional optimization, individualized exercise programs, pharmacological therapies, psychosocial support, and treatment of the underlying disease. Emerging therapies targeting inflammatory and metabolic pathways show promising potential, although further clinical evidence is needed.

Conclusion: Early recognition and multidisciplinary intervention are essential for slowing disease progression, preserving muscle mass, improving functional capacity, enhancing quality of life, and optimizing clinical outcomes. Comprehensive patient-centered management remains the cornerstone of effective cachexia care.

Keywords: Cachexia, Anorexia, Cancer Cachexia, Chronic Disease, Malnutrition, Skeletal Muscle Wasting, Nutrition Therapy, Physical Rehabilitation, Inflammation, Multidisciplinary Care.

Introduction

Cachexia represents a complex metabolic syndrome that develops secondary to a wide range of chronic diseases and is distinguished by progressive depletion of skeletal muscle mass, frequently accompanied by substantial loss of adipose tissue. Unlike uncomplicated malnutrition or starvation, cachexia arises from intricate interactions between persistent systemic inflammation, neurohormonal dysregulation, and profound metabolic disturbances that collectively promote a sustained catabolic state. The syndrome is commonly encountered among individuals with advanced malignancies, chronic infectious diseases, chronic obstructive pulmonary disease (COPD), chronic kidney disease, congestive heart failure, and advanced inflammatory autoimmune disorders. These chronic conditions initiate inflammatory cascades characterized by increased production of proinflammatory cytokines and other mediators that disrupt normal protein synthesis, accelerate muscle proteolysis, enhance lipolysis, and impair physiological energy homeostasis. Consequently, affected patients experience continuous deterioration of body composition despite the availability of nutritional intake, reflecting the fundamental distinction between cachexia and simple

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Receive Date: 07 December 2025, Revise Date: 29 December 2025, Accept Date: 31 December 2025

caloric deprivation. The metabolic adaptations associated with cachexia extend beyond reductions in food consumption and involve significant alterations in substrate utilization and energy expenditure. As glucose availability becomes increasingly compromised, adipose tissue reserves are mobilized to provide alternative energy substrates, thereby promoting accelerated fat loss while skeletal muscle proteins undergo continuous degradation to meet metabolic demands. Simultaneously, chronic systemic inflammation contributes to gastrointestinal dysfunction, hormonal imbalance, anorexia, and impaired nutrient absorption, creating a self-perpetuating cycle of malnutrition and tissue wasting. These mechanisms explain why conventional nutritional supplementation alone rarely reverses cachexia or restores lean body mass. In patients who develop pronounced appetite suppression alongside progressive tissue wasting, the condition is recognized as anorexia-cachexia syndrome, a clinical entity characterized by the coexistence of metabolic abnormalities and severe reductions in dietary intake that collectively accelerate disease progression and functional decline [1][2][3].

The prevalence and clinical expression of cachexia vary considerably according to the underlying disease process, particularly among patients with malignant disorders. Individuals diagnosed with pancreatic, gastrointestinal, and lung malignancies demonstrate the highest incidence of cachexia, reflecting the aggressive metabolic consequences associated with these tumor types. Conversely, patients affected by breast cancer, sarcomas, and hematologic malignancies generally experience lower rates of cachexia, although disease progression may still predispose susceptible individuals to significant nutritional deterioration. Regardless of its primary etiology, cachexia exerts a profound negative influence on patients' physical performance, psychological well-being, and overall quality of life. Progressive muscle wasting reduces functional capacity, compromises independence in daily activities, diminishes tolerance to surgical procedures and systemic therapies, and is consistently associated with increased morbidity, treatment-related complications, and shortened survival across diverse patient populations [1][2].

Accurate identification of cachexia requires a comprehensive diagnostic framework that integrates clinical observations, biochemical measurements, anthropometric evaluation, and assessments of physical function. Owing to the multifactorial nature of the syndrome, numerous professional organizations have developed diagnostic definitions and management recommendations; however, complete international consensus has yet to be achieved. The American Society of Clinical Oncology (ASCO) characterizes cancer cachexia as a multifactorial syndrome involving persistent skeletal muscle loss that cannot be completely corrected through conventional nutritional support, ultimately leading to progressive functional impairment. According to these recommendations, diagnosis is established by documenting involuntary body weight loss exceeding 5% during a six-month period or weight loss greater than 2% in individuals already exhibiting sarcopenia or a body mass index (BMI) below 20 kg/m². Complementing these recommendations, the Society of Cachexia and Wasting Disorders has proposed diagnostic criteria applicable to non-cancer-related cachexia, requiring weight loss of at least 5% over six months together with a minimum of three clinical manifestations including fatigue, anorexia, diminished muscle strength, reduced fat-free mass, or biochemical evidence of systemic inflammation [3]. Similarly, the Asian Working Group for Cachexia emphasizes the presence of an underlying chronic disease in combination with weight loss exceeding 5% within six months or a BMI below 20 kg/m² accompanied by continuing weight loss greater than 2%. Their criteria additionally require at least one supportive finding, including anorexia manifested by reduced appetite or decreased dietary intake, impaired muscle strength measured through handgrip dynamometry, or elevated inflammatory biomarkers such as a C-reactive protein concentration exceeding 5 mg/L [4]. The biological mechanisms underlying cachexia involve intricate interactions among inflammatory mediators, endocrine abnormalities, mitochondrial dysfunction, altered protein metabolism, and disturbances in energy regulation. Persistent activation of inflammatory pathways stimulates excessive protein degradation while suppressing anabolic signaling responsible for muscle maintenance and regeneration. Concurrent metabolic alterations promote increased resting energy expenditure, insulin resistance, accelerated lipolysis, and impaired nutrient utilization, thereby intensifying tissue wasting despite nutritional intervention. These pathological processes progressively reduce muscle strength, physical endurance, immune competence, and organ function, ultimately contributing to poorer therapeutic responses and unfavorable clinical outcomes. As muscle depletion advances, patients experience increasing frailty, reduced treatment tolerance, prolonged hospitalization, and higher mortality, emphasizing the importance of recognizing cachexia during its earliest stages before irreversible physiological deterioration occurs [5].

Etiology

Cachexia develops as a consequence of persistent chronic diseases that generate sustained systemic inflammation, metabolic dysregulation, and progressive tissue catabolism. Rather than representing a disorder caused solely by inadequate nutritional intake, cachexia arises from complex interactions between the underlying disease process and the host's metabolic response. It is frequently observed in patients with advanced malignancies, chronic heart failure, chronic kidney disease, chronic obstructive pulmonary disease (COPD), human

immunodeficiency virus (HIV) infection, tuberculosis, and severe autoimmune disorders. These conditions promote profound alterations in energy metabolism, endocrine regulation, immune function, and protein turnover, creating a persistent catabolic state that progressively depletes skeletal muscle and adipose tissue despite nutritional support. The continuous activation of inflammatory pathways and neurohormonal responses disrupts the balance between anabolic and catabolic mechanisms, resulting in accelerated muscle protein degradation, impaired protein synthesis, increased lipolysis, and progressive functional decline. Cancer-associated cachexia is among the most extensively investigated forms of the syndrome because of its high prevalence and substantial impact on patient survival and treatment outcomes. In many individuals, the primary tumor itself initiates the metabolic disturbances responsible for cachexia, although anticancer therapies such as chemotherapy and radiotherapy may further aggravate tissue wasting through treatment-related inflammation, gastrointestinal toxicity, reduced appetite, and impaired nutrient absorption. Tumor progression stimulates systemic inflammatory responses while simultaneously producing metabolic alterations that favor continuous nutrient consumption by malignant cells. Mechanical complications including gastrointestinal obstruction, impaired swallowing, organ dysfunction, and reduced digestive capacity may additionally limit food intake, thereby worsening nutritional deterioration. At the molecular level, several biological mediators contribute to cachexia, including proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), together with proteolysis-inducing factor (PIF) and lipid-mobilizing factor. These mediators promote inflammatory activation, stimulate skeletal muscle proteolysis, enhance adipose tissue breakdown, suppress muscle protein synthesis, and intensify metabolic inefficiency, ultimately accelerating the progression of cachexia [6][1][2].

An important metabolic mechanism contributing to cancer cachexia is the Warburg effect, a phenomenon in which malignant cells preferentially utilize aerobic glycolysis despite the availability of adequate oxygen. This altered metabolic pathway enables rapidly proliferating tumor cells to consume large quantities of glucose while producing excessive amounts of lactate. The lactate is subsequently transported to the liver, where it undergoes conversion back into glucose through the Cori cycle, a process requiring considerable energy expenditure by the host. Newly synthesized glucose then re-enters the circulation and is repeatedly utilized by tumor cells, creating a continuous cycle that favors tumor growth while progressively exhausting the body's energy reserves. This metabolic inefficiency substantially increases total energy expenditure, accelerates depletion of carbohydrate, lipid, and protein stores, and contributes directly to progressive muscle wasting and weight loss observed in patients with advanced malignancy [7]. Although cancer remains the leading cause of cachexia, similar pathogenic mechanisms occur in numerous chronic nonmalignant diseases characterized by persistent immune activation and systemic inflammation. Chronic infectious diseases, including tuberculosis, HIV infection, and several viral illnesses, induce prolonged immune dysregulation that maintains elevated inflammatory activity and disrupts normal metabolic homeostasis. Likewise, patients with chronic heart failure and COPD frequently exhibit persistently elevated concentrations of inflammatory biomarkers that stimulate protein degradation and impair normal tissue repair. Over time, these inflammatory and metabolic abnormalities produce negative energy balance, increased resting energy expenditure, progressive loss of skeletal muscle and adipose tissue, declining physical function, and worsening clinical outcomes, highlighting the shared biological pathways that underlie cachexia across diverse chronic diseases [7].

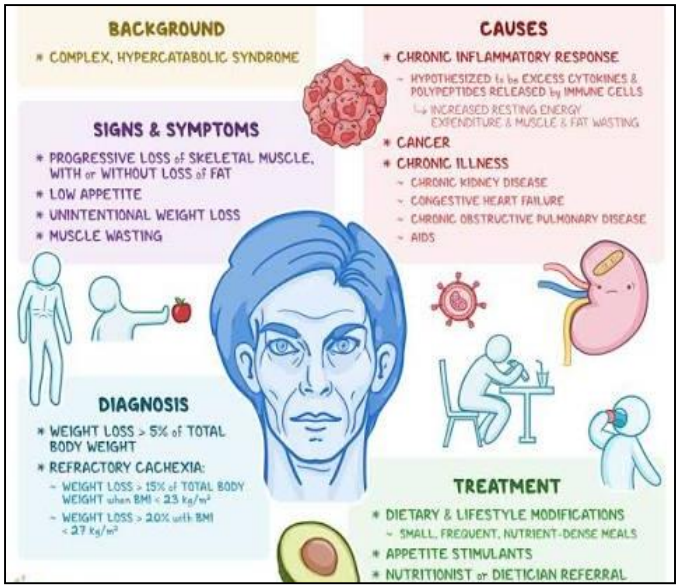

Figure 1: Cachexia.

Epidemiology

The epidemiological characteristics of cachexia vary considerably according to the underlying chronic disease, disease severity, patient demographics, and healthcare setting. Because cachexia is a syndrome rather than a single disease entity, its prevalence and clinical burden differ substantially across medical conditions associated with chronic inflammation and progressive metabolic dysfunction. The increasing global incidence of chronic diseases, coupled with population aging and improvements in survival among patients with long-term illnesses, has contributed to a growing number of individuals living with cachexia. In industrialized countries, the prevalence of cachexia is estimated to

affect approximately 9 million individuals, representing nearly 0.5% to 1% of the general population. These estimates are expected to increase steadily as the prevalence of cancer, cardiovascular disease, chronic respiratory disorders, chronic kidney disease, and other debilitating conditions continues to rise worldwide. Consequently, cachexia has emerged as an important public health concern because of its association with impaired quality of life, increased healthcare utilization, prolonged hospitalization, and elevated mortality rates. Among all underlying disorders, advanced malignancy represents the most common clinical setting in which cachexia develops. Approximately 50% to 80% of patients with advanced cancer experience varying degrees of cachexia during the course of their illness, although prevalence differs markedly according to tumor type, anatomical location, and disease stage. The syndrome is particularly common among patients with pancreatic, gastric, and esophageal cancers, where profound metabolic disturbances, gastrointestinal dysfunction, and reduced nutritional intake frequently occur early in the disease process. Gastrointestinal malignancies generally induce malnutrition and cachexia much earlier than breast, lung, or renal cancers because of their direct effects on digestion, nutrient absorption, gastrointestinal motility, and appetite regulation. As cancer progresses, systemic inflammation and tumor-induced metabolic alterations further accelerate muscle wasting and weight loss, making cachexia one of the leading contributors to cancer-related morbidity and mortality [8][9][10].

Cachexia is also highly prevalent among individuals with advanced nonmalignant chronic diseases. In patients with end-stage heart failure and chronic kidney disease, reported prevalence ranges from approximately 5% to 15%, with annual mortality rates reaching 20% to 30%. Similar prevalence estimates have been reported among patients with advanced chronic obstructive pulmonary disease (COPD), whose annual mortality is estimated to range between 10% and 15%. Persistent inflammation, increased resting energy expenditure, reduced physical activity, hormonal disturbances, and impaired nutritional intake collectively contribute to progressive muscle wasting in these populations [11]. Likewise, approximately 40% of hospitalized patients living with acquired immunodeficiency syndrome (AIDS) experience malnutrition, an essential component of cachexia, while long-term antiretroviral therapy may further contribute to alterations in body composition and skeletal muscle loss [12][13]. These epidemiological findings demonstrate that cachexia constitutes a major complication across a broad spectrum of chronic illnesses rather than being limited to oncology. The substantial prevalence, high mortality, and profound impact on functional capacity emphasize the importance of routine nutritional assessment, early diagnosis, multidisciplinary management, and preventive strategies. As the global burden of chronic diseases continues to expand with increasing life expectancy, timely recognition and targeted interventions for cachexia will become increasingly essential for improving patient outcomes, preserving functional independence, and reducing healthcare costs.

Pathophysiology

The pathophysiology of cachexia is highly complex and involves the interaction of inflammatory, metabolic, neuroendocrine, immunological, and gastrointestinal mechanisms that collectively produce progressive wasting of skeletal muscle and adipose tissue. Although cachexia develops in association with diverse chronic diseases, including malignancies, chronic heart failure, chronic kidney disease, chronic obstructive pulmonary disease, acquired immunodeficiency syndrome, and autoimmune disorders, these conditions converge on a common biological pathway characterized by persistent systemic inflammation, disrupted energy metabolism, and profound alterations in protein and lipid homeostasis. Unlike starvation, in which adaptive metabolic responses preserve lean body mass as much as possible, cachexia is marked by uncontrolled catabolism that persists despite adequate nutritional intake. Consequently, patients experience continuous reductions in body weight, skeletal muscle mass, physical performance, and physiological reserve, leading to progressive functional impairment and poorer clinical outcomes [1]. Persistent systemic inflammation represents the central mechanism responsible for the initiation and progression of cachexia. Chronic diseases stimulate continuous activation of both innate and adaptive immune responses, resulting in excessive production of inflammatory mediators that profoundly alter normal cellular metabolism. Among the most significant mediators are tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), which act synergistically to promote tissue catabolism while suppressing anabolic pathways responsible for muscle maintenance and repair. These cytokines stimulate proteolytic pathways within skeletal muscle, inhibit muscle protein synthesis, enhance lipolysis, and impair mitochondrial function, thereby reducing the efficiency of cellular energy production. Simultaneously, persistent inflammatory signaling increases resting energy expenditure by activating the sympathetic nervous system, producing a hypermetabolic state in which caloric requirements exceed nutritional intake. This imbalance accelerates depletion of endogenous energy stores and contributes directly to progressive loss of both muscle and adipose tissue [6].

In cancer-associated cachexia, the inflammatory response is amplified by factors released from both malignant cells and the host immune system. Tumor cells actively secrete numerous mediators that alter systemic metabolism to support their own proliferation while simultaneously

promoting host tissue degradation. These mediators include proteolysis-inducing factor (PIF), lipid-mobilizing factor, ciliary neurotrophic factor, leukemia inhibitory factor, and interferon-gamma, all of which contribute to metabolic dysfunction and progressive wasting. Together with inflammatory cytokines produced by activated immune cells, these substances stimulate muscle protein degradation, accelerate adipose tissue breakdown, induce anorexia, impair glucose utilization, and increase whole-body energy expenditure. As disease progresses, patients develop insulin resistance, reduced circulating insulin concentrations, elevated cortisol and glucagon levels, increased resting heart rate, fever, and anemia, all of which intensify catabolism and further compromise nutritional status [14][15][10]. The immune system plays a fundamental role in perpetuating the chronic inflammatory environment characteristic of cachexia. Activated macrophages, type 1 helper T lymphocytes, and myeloid-derived suppressor cells continuously release procachectic cytokines that maintain inflammatory activation throughout the disease course. At the same time, tumor-derived proteolysis-inducing factor enhances adrenergic stimulation, increasing resting metabolic rate and promoting excessive energy consumption. Skeletal muscle serves as the principal site of tissue depletion because it represents the body's largest reservoir of protein available for metabolic demands. Within muscle fibers, inflammatory cytokines and proteolysis-inducing factor activate the nuclear factor kappa B (NF-κB) signaling pathway, a transcription factor that regulates numerous genes involved in inflammation and protein degradation. Activation of this pathway markedly increases protein turnover by accelerating proteolysis while simultaneously suppressing pathways responsible for muscle protein synthesis. As a result, muscle loss progresses continuously despite adequate dietary protein intake, explaining why nutritional therapy alone is generally insufficient to reverse cachexia [10].

Neuroendocrine dysfunction further contributes to the development and persistence of cachexia through disruption of central appetite regulation and hormonal homeostasis. Chronic inflammation directly affects hypothalamic function, altering neural circuits responsible for regulating hunger, satiety, and energy balance. Proinflammatory cytokines, particularly TNF-α and IL-1β, induce hypothalamic inflammation that suppresses appetite while simultaneously increasing metabolic rate. These inflammatory processes interfere with the hypothalamic-pituitary-adrenal axis, resulting in enhanced catabolic hormonal signaling and diminished responsiveness to appetite-stimulating neuropeptides, including neuropeptide Y. Consequently, affected individuals experience persistent anorexia, reduced food intake, early satiety, and diminished motivation to eat, all of which exacerbate negative energy balance and accelerate tissue wasting [16]. Hormonal abnormalities further intensify the catabolic state characteristic of cachexia. Reduced testosterone concentrations, particularly in male patients, impair muscle protein synthesis while increasing protein degradation, thereby promoting progressive muscle atrophy. Chronic inflammation also disrupts the hypothalamic-growth hormone-insulin-like growth factor-1 (IGF-1) axis. Although circulating growth hormone concentrations may remain normal or even increase, inflammatory mediators induce peripheral growth hormone resistance, resulting in reduced production and biological activity of IGF-1. Because IGF-1 is a critical anabolic hormone responsible for stimulating muscle growth and inhibiting proteolysis, its deficiency substantially impairs muscle regeneration and accelerates skeletal muscle breakdown. Importantly, these metabolic abnormalities persist even when patients receive adequate caloric and protein intake, emphasizing that cachexia results primarily from dysregulated metabolism rather than simple nutritional deficiency [17].

Gastrointestinal dysfunction represents another major contributor to the pathophysiology of cancer-associated cachexia by limiting nutrient intake and reducing digestive efficiency. Many patients experience alterations in taste and olfactory perception that diminish food enjoyment and reduce appetite. Malignancies involving the oral cavity, pharynx, esophagus, stomach, or upper gastrointestinal tract frequently impair swallowing and oral intake through mechanical obstruction or pain. Tumors affecting the pancreas, liver, bowel, or peritoneum may produce intestinal obstruction, delayed gastric emptying, or impaired gastrointestinal motility, leading to early satiety, nausea, abdominal discomfort, and decreased food consumption. Pancreatic insufficiency reduces digestive enzyme production, causing fat malabsorption and nutrient deficiencies that further aggravate weight loss. Together, these gastrointestinal abnormalities substantially impair nutritional status and reinforce the progression of cachexia [18][19]. Cancer therapies frequently exacerbate these gastrointestinal disturbances and accelerate nutritional deterioration. Chemotherapeutic agents such as cisplatin and doxorubicin commonly induce nausea, vomiting, mucositis, taste alterations, and olfactory disturbances that significantly reduce oral intake. Similarly, immune checkpoint inhibitors and other immunotherapeutic agents may produce gastrointestinal toxicity, further limiting nutritional consumption. Radiotherapy directed toward the head and neck often results in stomatitis, xerostomia, mucosal ulceration, and painful swallowing, whereas abdominal irradiation may cause anorexia, nausea, vomiting, diarrhea, intestinal inflammation, and

malabsorption. These treatment-related adverse effects frequently persist throughout therapy, making adequate nutritional intake increasingly difficult and intensifying both anorexia and cachexia. Moreover, the psychological burden associated with chronic illness, including anxiety, depression, emotional distress, and social isolation, further suppresses appetite and contributes to continued weight loss, demonstrating that psychological factors also participate in the multifactorial pathogenesis of cachexia [20][21][22].

History and Physical

The clinical evaluation of patients with suspected cachexia begins with a comprehensive medical history and detailed physical examination, both of which are essential for identifying the syndrome, determining its severity, and establishing the relationship between progressive weight loss and the underlying chronic disease. Because cachexia most frequently develops during the advanced stages of malignancy or other long-standing illnesses, including chronic heart failure, chronic kidney disease, chronic obstructive pulmonary disease, chronic infections, and inflammatory disorders, healthcare professionals should maintain a high level of clinical suspicion when evaluating patients with these conditions. A careful history should emphasize the onset, duration, and progression of weight loss while distinguishing unintentional weight reduction from intentional dietary modification. Patients commonly report persistent weight loss despite consuming what appears to be an adequate or even increased amount of food, reflecting the metabolic abnormalities that characterize cachexia rather than simple nutritional deficiency. Additional symptoms frequently include reduced appetite, early satiety, diminished food intake, altered taste perception, and persistent anorexia, all of which contribute to worsening nutritional status and progressive tissue wasting [3][23]. Functional decline is another prominent feature identified during clinical history taking. Patients often describe increasing fatigue, generalized weakness, reduced endurance, impaired exercise tolerance, and progressive difficulty performing activities of daily living that were previously completed without assistance. Many individuals report declining mobility, inability to maintain employment or household responsibilities, and reduced participation in social activities because of severe physical exhaustion. Fatigue may result from multiple contributing factors, including chronic systemic inflammation, skeletal muscle loss, metabolic disturbances, anemia associated with the underlying disease, and the physiological consequences of cachexia itself. These symptoms significantly diminish quality of life and frequently indicate advanced disease progression [3][23].

Physical examination provides important objective evidence supporting the diagnosis of cachexia. The most characteristic finding is generalized skeletal muscle wasting, which is particularly evident in the upper and lower extremities, producing a markedly thin and frail appearance. Muscle weakness is readily demonstrated by reduced handgrip strength and decreased overall functional performance. Progressive loss of subcutaneous adipose tissue results in prominent bony landmarks, including the clavicles, shoulders, ribs, scapulae, hips, and facial bones, giving patients a gaunt appearance. Anthropometric assessment commonly reveals a reduced body mass index, frequently below 20 kg/m^2, together with substantial involuntary weight loss over recent months. The examination should also assess for clinical manifestations of the underlying chronic disease, such as pallor secondary to anemia, peripheral edema associated with cardiac or renal dysfunction, lymphadenopathy, hepatomegaly, splenomegaly, or other forms of organomegaly when clinically indicated. A comprehensive history and physical examination therefore provide the foundation for early recognition of cachexia, facilitate assessment of disease severity, and guide subsequent diagnostic evaluation and multidisciplinary management.

Evaluation

The evaluation of cachexia requires a comprehensive and multidisciplinary approach that extends beyond confirming weight loss to identifying the underlying disease, determining the severity of metabolic dysfunction, evaluating nutritional status, assessing functional impairment, and estimating prognosis. Following a detailed medical history and thorough physical examination, clinicians should investigate both the primary condition responsible for the syndrome and the extent of its systemic consequences. Early recognition is particularly important because timely intervention may delay disease progression, preserve functional capacity, improve treatment tolerance, and enhance quality of life. Since cachexia represents a dynamic clinical process rather than a single event, continuous assessment throughout the course of the underlying disease is essential for monitoring progression and evaluating the effectiveness of therapeutic interventions. To facilitate clinical decision-making, cachexia is commonly classified into three progressive stages: pre-cachexia, cachexia, and refractory cachexia. These stages reflect increasing severity of metabolic abnormalities, nutritional deterioration, and functional decline while providing valuable prognostic information. Patients with pre-cachexia typically demonstrate early metabolic alterations, anorexia, and involuntary weight loss of less than 5%, representing a potentially reversible stage if appropriate interventions are implemented promptly. Established cachexia is characterized by unintentional weight loss exceeding 5% over a relatively short period or the presence of a body mass index below 20 kg/m^2 accompanied by ongoing skeletal muscle loss, fatigue, anorexia, and measurable impairment in physical function. The most advanced stage, refractory cachexia, occurs predominantly in patients with end-

stage disease, especially advanced malignancies, in whom severe muscle wasting and progressive weight loss persist despite comprehensive therapeutic measures. At this stage, anticancer treatment is generally ineffective, functional decline is profound, and predicted survival is commonly limited to approximately three to six months [24].

Comprehensive nutritional assessment constitutes a fundamental component of cachexia evaluation because nutritional status significantly influences clinical outcomes and therapeutic planning. Assessment should include detailed documentation of habitual dietary intake, appetite, swallowing ability, gastrointestinal symptoms, recent changes in food consumption, and factors limiting adequate nutrition. Daily caloric and protein intake should be estimated and compared with individualized nutritional requirements based on age, sex, body weight, physical activity, disease burden, and the elevated resting energy expenditure characteristic of cachexia. This evaluation assists clinicians in identifying nutritional deficiencies, estimating energy requirements, and designing individualized nutritional interventions aimed at minimizing further tissue loss and supporting overall clinical management. Objective assessment of body composition provides valuable information regarding the degree of muscle wasting and depletion of adipose tissue. Anthropometric measurements combined with advanced body composition analysis techniques enable clinicians to quantify changes in lean body mass and fat distribution with greater precision than body weight alone. Bioelectrical impedance analysis and dual-energy X-ray absorptiometry (DEXA) are widely used methods for evaluating skeletal muscle mass, body fat percentage, and changes occurring throughout disease progression. DEXA is particularly valuable because it accurately measures regional and total body composition, allowing clinicians to monitor the progression of cachexia and evaluate responses to nutritional and pharmacological interventions over time. These objective measurements improve diagnostic accuracy and facilitate longitudinal assessment of disease severity.

Evaluation of muscle function is equally important because functional impairment frequently precedes substantial changes in body weight and serves as an independent predictor of prognosis. Handgrip strength, measured using a calibrated hand dynamometer, is one of the most reliable and widely accepted indicators of muscle function in patients with cachexia. Grip strength values below 20 kilograms in men and below 14 kilograms in women indicate significant impairment of muscle performance and are associated with increased morbidity, reduced physical independence, and poorer survival outcomes [25]. Functional performance should also be assessed using validated physical performance tests, including the Stair Climb Power Test, the Timed Up and Go Test, and the Six-Minute Walk Test. These assessments evaluate mobility, muscular endurance, balance, exercise capacity, and overall physical function, providing objective measures that correlate closely with disease severity and functional decline [26]. Additional validated assessment tools include the Patient-Generated Subjective Global Assessment, which integrates nutritional and clinical findings, and the Phase Angle Test derived from bioelectrical impedance analysis. A reduced phase angle reflects diminished cellular integrity, reduced muscle mass, altered fluid distribution, and severe malnutrition, making it a valuable prognostic indicator in patients with cachexia [27]. Laboratory investigations provide important complementary information regarding the metabolic, inflammatory, hematological, and endocrine abnormalities associated with cachexia. Measurements of serum albumin, prealbumin, and transferrin help evaluate protein reserves and nutritional status, although their interpretation should consider the influence of inflammation and underlying disease. Inflammatory biomarkers, particularly C-reactive protein, serve as indicators of systemic inflammation and correlate with disease severity, ongoing muscle wasting, and overall prognosis. A complete blood count is essential for identifying anemia, infection, or other hematological abnormalities that may contribute to fatigue and functional impairment. Comprehensive metabolic panels, including serum electrolytes and liver and kidney function tests, assist in detecting organ dysfunction, metabolic disturbances, and complications related to the underlying disease. Hormonal evaluation, including measurements of testosterone, thyroid hormones, and other endocrine parameters when clinically indicated, may identify hormonal deficiencies that exacerbate muscle wasting, fatigue, and weight loss. Furthermore, assessment of micronutrient status is recommended because deficiencies of iron, vitamin D, vitamin B12, folate, and other essential nutrients are common among patients with chronic diseases and may worsen the clinical manifestations of cachexia.

Treatment / Management

Management of cachexia requires a comprehensive, multidisciplinary strategy because no single intervention can completely reverse the syndrome. Effective treatment combines nutritional support, structured physical rehabilitation, pharmacologic therapy, and management of the underlying disease. Early recognition is particularly important, as interventions initiated during the pre-cachexia stage are more likely to preserve muscle mass, improve functional capacity, and enhance quality of life. Treatment plans should be individualized according to the patient's underlying illness, disease stage, nutritional status, physical

performance, prognosis, and personal goals. In patients with cancer, definitive treatment of the primary tumor offers the greatest opportunity to prevent or delay cachexia. When curative treatment is not feasible, management focuses on slowing disease progression, reducing symptoms, preserving functional independence, and optimizing overall well-being through coordinated nutritional, medical, and rehabilitative care.[28][29][30] Early nutritional assessment is a cornerstone of cachexia management. Current recommendations from the American Society of Clinical Oncology (ASCO) and the European Society for Clinical Nutrition and Metabolism (ESPEN) advocate routine nutritional screening for patients at risk, with evaluation of body composition, inflammatory status, resting energy expenditure, dietary intake, and physical function to guide individualized interventions.[3][30] Nutritional therapy emphasizes high-energy, high-protein diets supported by fortified foods and oral nutritional supplements when required. Commercial supplements generally provide concentrated calories and protein, while recommended protein intake ranges from 1.0 to 1.5 g/kg/day for most patients, although lower protein intake is advised in advanced renal failure.[10][3][31] Adequate vitamin D intake supports muscle protein synthesis, skeletal health, and metabolic function, particularly in patients undergoing cancer therapy.[32] Nutritional optimization before and during chemotherapy may reduce treatment-related complications and improve clinical outcomes, although improvements in nutritional markers do not always translate into reduced chemotherapy toxicity.[33]

Dietary management should remain individualized and patient-centered, considering appetite, gastrointestinal tolerance, food preferences, treatment-related adverse effects, and socioeconomic factors. Registered dietitians play an essential role in providing evidence-based dietary counseling while discouraging restrictive or unproven dietary approaches that may worsen nutritional deficits.[3] Patients are commonly encouraged to consume frequent, energy-dense meals, maintain adequate hydration, and use vitamin and mineral supplements to meet recommended daily requirements. Homemade nutritional supplements may improve adherence in some patients, while room-temperature or sour foods are often better tolerated by individuals experiencing taste alterations or anorexia.[35] Although experimental studies have suggested that ketogenic diets may alter tumor metabolism, current clinical evidence remains insufficient to support their routine use in patients with cachexia.[34] Likewise, routine enteral tube feeding or total parenteral nutrition is not recommended unless specific clinical indications exist because available evidence has not demonstrated consistent improvements in survival or quality of life, and these interventions carry risks including infection and catheter-related complications.[3][36] Among nutritional supplements, omega-3 fatty acids, particularly eicosapentaenoic acid (EPA), have attracted considerable interest because of their anti-inflammatory properties. EPA may reduce cytokine production and modestly improve body weight and lean body mass when administered at doses between 1.8 and 2.2 g daily. However, gastrointestinal intolerance, hepatic dysfunction, and bleeding complications may occur, and current evidence remains insufficient to recommend routine supplementation in all patients with cachexia.[3]

Exercise represents another essential component of comprehensive cachexia management. Physical activity counteracts many of the metabolic abnormalities responsible for muscle wasting by stimulating protein synthesis, improving insulin sensitivity, reducing inflammation, and preserving skeletal muscle mass.[37] Current recommendations from ESPEN and the European Society for Medical Oncology advocate moderate aerobic and resistance exercise programs tailored to each patient's functional capacity and medical condition.[19][38] Supervised exercise improves muscle strength, cardiorespiratory fitness, bone health, physical performance, and psychological well-being while reducing fatigue, depression, and treatment-related distress.[39] Exercise initiated early during cancer treatment appears particularly beneficial for maintaining functional independence and reducing long-term disability.[40] Resistance training is generally more effective than aerobic exercise alone for preserving lean body mass and muscle strength, although combining both modalities provides broader physiological benefits. Home-based supervised exercise programs have demonstrated improved adherence compared with hospital-based training, highlighting the importance of individualized exercise prescriptions that accommodate patient preferences and physical limitations.[41] Clinical trials have shown that supervised exercise during chemotherapy can maintain physical performance and cardiorespiratory fitness, although improvements in overall quality of life have been inconsistent.[42][43] Despite these benefits, many patients experience substantial barriers to physical activity, including severe fatigue, muscle weakness, pain, impaired mobility, low energy levels, and psychological distress. These challenges emphasize the importance of carefully supervised rehabilitation programs designed by physical therapists and exercise specialists to ensure safety while maximizing functional outcomes.[44][45]

Pharmacologic therapy serves as an adjunct to nutritional and exercise interventions rather than a replacement for them. Current medications primarily target appetite stimulation, reduction of inflammation, preservation of muscle mass, or modulation of metabolic abnormalities. Although none of these agents completely reverses cachexia, several therapies improve symptoms and enhance quality of life.

Appetite stimulants remain among the most commonly prescribed medications. Progesterone analogs such as megestrol acetate and medroxyprogesterone acetate improve appetite and promote weight gain primarily through increased fat deposition. Megestrol acetate has received regulatory approval for AIDS-associated cachexia and is frequently prescribed off-label for cancer-related cachexia despite risks including thromboembolism, fluid retention, and increased mortality.[3] Corticosteroids such as dexamethasone provide short-term appetite improvement but prolonged administration is limited by adverse effects including immunosuppression, osteoporosis, hypertension, and fluid retention.[46][47] Anamorelin, a ghrelin receptor agonist, has demonstrated improvements in appetite, body weight, lean body mass, and patient-reported quality of life in clinical trials, although concerns regarding hyperglycemia and cardiovascular adverse events have prevented FDA approval.[3][48][49] Olanzapine has also shown favorable effects on appetite, weight gain, and chemotherapy-induced nausea with relatively few adverse effects, whereas evidence supporting mirtazapine remains less robust despite its usefulness in patients with concurrent depression.[50][51][52] Several anabolic therapies aim to preserve or restore skeletal muscle mass. Nandrolone decanoate has demonstrated improvements in muscle mass, physical function, and body weight among patients with cancer and HIV-associated cachexia, although benefits in overall survival have not been established and treatment may produce hepatic toxicity, cardiovascular complications, and fluid retention.[3][53] Enobosarm, a selective androgen receptor modulator, has shown promising anabolic effects on skeletal muscle in early clinical studies but remains investigational.[3] Recombinant human growth hormone has improved lean body mass and physical function in HIV-associated cachexia and experimental models of chronic kidney disease, although high treatment costs and adverse effects including edema, arthralgia, and hyperglycemia limit widespread clinical use.[54][55]

Targeting inflammatory pathways represents another promising therapeutic strategy because chronic inflammation is central to the pathogenesis of cachexia. Thalidomide suppresses TNF-α production and has demonstrated improvements in appetite and lean body mass when combined with other therapies, although sedation, constipation, and other toxicities restrict routine use.[56][3] Biological agents targeting inflammatory cytokines, including infliximab, adalimumab, and monoclonal antibodies directed against interleukin-1 alpha, have shown encouraging early results by reducing inflammatory activity, increasing lean body mass, and improving patient-reported symptoms. Nevertheless, larger clinical trials remain necessary before these therapies can be recommended for routine clinical practice.[57][58] Similarly, nonsteroidal anti-inflammatory drugs such as indomethacin and celecoxib have been investigated, but current evidence does not support their routine use outside research settings.[59][3] Emerging metabolic therapies seek to directly inhibit the molecular pathways responsible for muscle wasting. Myostatin inhibitors have demonstrated preservation of muscle mass and improved muscle function in preclinical studies by removing inhibitory signals that suppress muscle growth.[62][63] Bimagrumab, which blocks activin type II receptors involved in myostatin signaling, has also shown encouraging anabolic effects but remains investigational.[64][65] Beta-hydroxy-beta-methylbutyrate (HMB), a metabolite of leucine, has demonstrated anabolic properties by stimulating protein synthesis and reducing muscle protein degradation, although additional clinical evidence is required before routine use can be recommended.[66] Supportive therapies primarily address symptoms associated with cachexia rather than the underlying metabolic abnormalities. Current evidence does not support routine use of cannabinoids, cyproheptadine, or similar appetite stimulants because they have not consistently improved appetite, body weight, or quality of life compared with established therapies.[67][68] Metoclopramide may relieve nausea, vomiting, delayed gastric emptying, and gastroparesis, thereby facilitating oral intake in selected patients, although it does not directly influence the metabolic processes responsible for cachexia.[69][3]

Conclusion:

Cachexia represents one of the most challenging complications of chronic diseases because it extends beyond simple malnutrition and reflects a complex interaction between systemic inflammation, metabolic dysregulation, hormonal alterations, and progressive tissue catabolism. Its multifactorial nature contributes to continuous skeletal muscle loss, declining physical function, impaired treatment tolerance, diminished quality of life, and increased mortality across patients with cancer, chronic cardiovascular, respiratory, renal, infectious, and autoimmune diseases. Early identification through comprehensive clinical evaluation, nutritional assessment, body composition analysis, laboratory investigations, and functional performance testing is essential to prevent irreversible physiological deterioration and improve long-term outcomes. Successful management requires an integrated multidisciplinary approach that combines individualized nutritional support, structured exercise rehabilitation, pharmacological interventions, psychosocial care, and optimal treatment of the underlying disease. Collaboration among physicians, nurses, clinical nutritionists, physical therapists, radiology professionals, epidemiologists, and public

health specialists is fundamental to addressing the diverse biological and functional consequences of the syndrome. Although current therapies primarily slow disease progression rather than reverse cachexia, advances in anti-inflammatory, anabolic, and metabolic-targeted treatments offer promising opportunities for future clinical practice. Continued research, early screening, patient-centered interventions, and coordinated multidisciplinary care remain essential for preserving functional independence, improving treatment tolerance, enhancing quality of life, and reducing the substantial healthcare burden associated with anorexia and cachexia.

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