[97]. As a matter of fact, there are only very few clinical trials investigating the impact of exercise training in cachexia [97]. A few small studies have shown that exercise training leads to changes in body composition [97]. Investigations with larger cohorts and hard end points are still missing [97]. Most of the research concerning exercise training and cachexia has been done in the field of cancer cachexia, preferably with animal models [97]. It is still under discussion as to which patients with refractory cachexia might profit from mild physical activity intervention [97]. Counseling patients on cancer-related fatigue can encourage patients to maintain a minimal form of activity and slow down the decrease in physical function and quality of life [97].

Nutritional counseling

The management of cachexia in advanced cancer patients should focus on maximizing oral intake by allowing the patient flexibility in type, quantity, and timing of meals [99]. Nutritional counseling has been reported to improve nutritional intake in patients undergoing chemotherapy [179]. Moreover, it has also been shown to improve quality of life in patients undergoing radiotherapy [180]. However, the influence of counseling on reducing psychological distress in patients with a palliative care setting remains to be established [97].

Adequate education and counseling should also address the concerns of family members who may worry that their relative appears to be 'starving to death' by underscoring the differences between starvation and cachexia [97]. The appropriate provision of counseling, for example dietetic consultation or information sheet has not been established for patients with refractory cachexia [97]. Professional health care teams of oncology physicians, nurses, and dietitians can diagnose specific needs and plan individualized treatment for improved nutritional health with patients and their families [97]. Counseling, which any member of the health care team may provide, is an effective and inexpensive intervention and should be combined with other nutritional interventions [181]. Nursing interventions to counteract cachexia should be aimed at minimizing the negative factors of nausea, vomiting, diarrhea, pain, fatigue, changes in taste or food preferences that may influence appetite [99].

Even if there is no evidence that nutritional counseling improves overall quality of life or physical functioning in patients with refractory cancer cachexia, there is a strong support by experts that nutritional counseling can aid cancer patients and family members to understand the changes, and to differentiate what they can improve and where the limitations of nutrition [97, 181]. However this requires advanced psychological and nutritional knowledge on the part of the counselors [97].

Palliative care and mental health support

The health care team should ensure that patients' physical symptoms (e.g., pain, fatigue, breathlessness) are being assessed and managed effectively, as this may improve appetite, ability to take up food, and general well-being [97]. Psychological distress and psychiatric disorders are common among patients with cancer and have a prevalence ranging from 10 to 79 % [99]. These problems are also as common among the family members of people with cancer [99]. Anorexia and cachexia may result in secondary depression, or depression itself may be a prime contributor to anorexia and subsequent weight loss. Benzodiazepines can be helpful for persistent fear and anxiety, and antidepressant drugs are increasingly used in patients with cancer with comorbid depression [99].

The use of psychological and behavioral interventions (e.g., relaxation, hypnosis, and short-term group psychotherapy) in cancer is increasing and recent studies have suggested that some of these techniques may affect quality of life and, perhaps, survival rates [99]. However, there is no evidence that psychotherapeutic interventions have an effect on nutritional status [97]. Moreover, for refractory cachexia, reduced performance status and short prognosis may preclude this intervention [97].

Caring for a person with advanced disease can be physically and emotionally stressful [97]. Caregivers often note that when friction occurs between themselves and the individual for whom they are caring, it often occurs over the issue of eating [99]. These caregivers report that they find it hard to cope with the patient who relentlessly loses weight and strength and yet persistently refuses adequate food intake [99]. Effective communication with patients and their families is essential and is an important component of treatment [99].

Managing side effects

Many cancer interventions will exacerbate already reduced energy and nutrient intake [80]. Surgical patients may be fasted for prolonged periods peri-operatively, and both chemotherapy and radiotherapy can induce side-effects such as anorexia, nausea, vomiting, mucositis, taste change, or lethargy [80]. Symptoms will depend on the nature and course of the chemotherapeutic drugs being used and the location, volume, and dose of radiotherapy [80]. Some cytotoxic drugs may even generate their own cachexia-like side-effects [82]. For example, antitubulin taxanes induce greater loss of body weight in tumor-bearing mice than in healthy mice, even when the agents significantly reduce tumor growth [80]. The complex interaction between nutrition, cachexia, and chemotherapy still requires elucidation [80, 182, 183].

Adverse Effects of Chemotherapy and Radiation

Although chemotherapy and radiation treatments are usually directed by a subspecialist, the physician must be aware of potential adverse effects and, in some practice settings, may be called on to manage them [184].

Approximately 70–80 % of patients treated with chemotherapy experience nausea and vomiting [185], which may be acute (occurring within a few hours after chemotherapy), delayed (occurring 24 or more hours after chemotherapy), breakthrough or refractory (occurring despite prophylactic treatment), or anticipatory (occurring before chemotherapy treatment). The emetogenic (vomit-inducing) potential of chemotherapeutic agents varies from mild to severe [186]. Drug dose, schedule and route of administration, and patient variability are also factors [184].

Antiemetic therapy is most effective if given before chemotherapy and maintained while the emetic potential of the agent continues. Oral formulations are as effective as parenteral or rectal routes if the patient is able to swallow and digest tablets. Lorazepam, metoclopramide, and prochlorperazine often are used for moderate- to low emetic-risk chemotherapy and for breakthrough nausea.

Currently, 5-HT antagonists (ondansetron, granisetron, dolasetron and palonosetron) are most widely used in practice for patients given chemotherapy with a moderate-to-high risk of gastrointestinal side effects. Trials with these agents indicate that they are highly effective in controlling acute nausea and vomiting associated with chemotherapy and have minimal adverse effects [187–189]. They are equally effective for acute nausea [190], but palonosetron, which has a much higher affinity for the 5-HT receptor and a longer half-life than the other 5-HT antagonists, is more effective than dolasetron in preventing delayed emesis [191]. The co-administration of dexamethasone improves the effectiveness of 5-HT antagonists in controlling acute emesis. However, one study found that adding a 5-HT antagonist to dexamethasone for the treatment of delayed nausea and vomiting did not result in an improved antiemetic effect over dexamethasone alone [184, 192]. Aprepitant, the first neurokinin-1 receptor antagonist, augments the activity of 5-HT antagonists and dexamethasone to inhibit acute and delayed emesis induced by cisplatin [184, 193, 194].

Nausea and vomiting can also occur following radiation treatment and are most likely in patients undergoing whole body or upper abdominal radiation [184]. Higher total dose of radiation, larger amount of tissue radiated, and a higher daily fraction of radiation are also factors in the severity of nausea and vomiting [184].

Fever and neutropenia in a patient undergoing chemotherapy are also common and should be treated promptly [184]. Fever in a patient undergoing chemotherapy is common and worrisome [184]. In the guidelines developed by the Infectious Diseases Society of America (IDSA) [195], fever is defined as a single oral temperature higher than 100.9 °F (38.3 °C) or an oral temperature of 100.4 °F (38.0 °C) or higher for more than 1 h.

An absolute neutrophil count less than 500 per mm^3 (0.5 × 109 per L) is defined as severe neutropenia. The severity of infection is inversely related to the neutrophil count, with the greatest risk of bacteremia at absolute neutrophil levels lower than 100 per mm^3 (0.1 × 109 per L) [196]. Evaluation of the patient with neutropenia includes physical examination (with attention to indwelling vascular access devices), laboratory data, radiographs, and blood and urine cultures.

No single antibiotic or antibiotic combination can be uniformly recommended for all febrile neutropenic patients [184]. Initial therapy is selected after considering the most likely potential infecting organism, site of infection, organ function (e.g., kidney, liver), medication allergies, and recent antibiotic treatment [184].

The most widely used outpatient antibiotic choice is an oral fluoroquinolone or amoxicillin/clavulanate [184]. Commonly used empiric intravenous antibiotic monotherapies include carbapenems (e.g., imipenem/cilastatin, meropenem), and extended-spectrum antipseudomonal cephalosporins (e.g., ceftazidime, cefepime). Dual therapy agents include an aminoglycoside with antipseudomonal penicillin (with or without a betalactamase inhibitor) or an extended-spectrum antipseudomonal cephalosporin; and ciprofloxacin with antipseudomonal penicillin [184].

According to IDSA and National Comprehensive Cancer Network guidelines, diagnostic reassessment should occur if fever does not improve in 3–4 days [195]. Although most patients with cancer-related febrile neutropenia will recover without major complications, involvement of a subspecialist should be considered when the patient's fever does not improve after 3 or 4 days of appropriate antimicrobial treatment or when the patient has septic shock, methicillin-resistant *Staphylococcus aureus* infection, or signs and symptoms of invasive fungal infection [184].

Cancer cachexia in special populations

Elderly

The management of cancer in the older person is an increasingly common problem, as 60 % of all neoplasms occur in individuals age 65 and older [197]. Cachexia is one of the major causes of weight loss in the elderly and numerous studies have shown that weight loss is associated with an increase in mortality [198–201]. Although body weight is easily measured, the evaluation of unintended

weight loss in long-term care facilities is difficult [202]. Whether anorexia and weight loss are reversible or unavoidable requires a careful clinical evaluation in the individual patient [203]. A structured approach to the differential diagnosis of malnutrition in long-term care was developed by the Council for Nutritional Clinical Strategies in Long- Term Care [203].

Additionally, muscle mass loss is characteristic of physical frailty and sarcopenia (age-related loss of muscle mass). Physical frailty has been characterized as a condition that results from reduced strength, reduced gait velocity, reduced physical activity, weight loss, and exhaustion. Thus, sarcopenia and frailty could be classified as cachectic conditions because they are associated with muscle mass loss.

Treating weight loss in the elderly can ameliorate many medical conditions. For example, rehabilitation time following post-hip fractures has been shown to decrease with nutritional supplementation [204]. In hospitalised geriatric patients, nutritional supplementation resulted in improvement in serum protein and, nutritional status, and decreased mortality [205]. In a subset of geriatric inpatients, low serum albumin with weight loss predicts those patients at highest risk for dying during the subsequent 2 years [206].

Moreover, in elderly patients with cachexia, medical, cognitive, and psychiatric disorders may diminish self-sufficiency in activities of daily living (e.g., grooming, ambulation), thus reducing health-related quality of life and increasing the frequency of secondary procedures, hospitalizations, and need for skilled nursing care [198, 199]. Increased understanding of the pathophysiology of geriatric cachexia in geriatric patients has resulted in effective and safe nutritional measures [206]. In particular, a better understanding of the role of proinflammatory cytokines (e.g., increased levels of negative regulatory cytokines) in cancer cachexia in the elderly may lead to pharmacological treatment targeted for this population [207].

The potential involvement of IL-6, TNF-α, IL-1, serotonin, PGE2 and other cytokines (e.g., IL-10, IL-4, IL-15) in the pathophysiology of aging, chronic diseases, and wasting calls for additional research on ways to suppress the secretion, dysregulation, or downstream effects of the pharmacotherapy for the treatment of cachexia in elderly [207]. Further investigation with specific nutritional manipulations, and the administration of specific steroids, neuropeptides, and peptide hormones is necessary [207].

Children

Anorexia and cachexia is commonly seen in pediatric patients that receive cancer treatment. The most prominent clinical feature of cachexia in children is growth failure [97], and weight loss or decreased growth are valuable indicators of malnutrition [208]. Growth is important for children because it is an essential feature of their health [208, 209]. However, criteria for weight loss or decreased growth have seldom been used in the assessment of nutritional status in children with cancer [208]. To date, weight loss is mainly described in the literature concerning failure to thrive [210, 211], but not for describing malnutrition [208].

Children appear to be at greater nutritional risk than adults because of high protein and energy requirements and limited caloric reserves [212]. Malnutrition is associated with an increased rate of infection in children with malignant neoplasms [212].

Given the increasing attention to evidence suggesting the negative impact of cachexia on the quality of life of children with cancer, it is necessary to develop a scale that targets the concerns of pediatric patients with cancer that is specific to anorexia and cachexia [212]. An appropriate scale must have sound psychometric properties, be user friendly, and monitor cachexia-related effects on quality of life over time [212].

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Review

Control of food intake and muscle wasting in cachexia☆

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ABSTRACT

Cachexia is characterized by anorexia, weakness, weight loss, and muscle wasting. Anorexia and muscle wasting are the key features of cachexia and they affect mortality, morbidity, and quality of life. Consistent studies have found that feeding-regulating peptides such as melanocortin, ghrelin, and leptin are related to muscle metabolism, and the balance of catabolism and anabolism in muscle is regulated in the hypothalamus, which also regulates appetite and energy expenditure. In cachexia, proinflammatory cytokines, such as TNF-α, IL-1, IL-6 and Angiotensin II induce muscle atrophy. The mechanism is suggested via upregulation of MuRF1 and MAFbx. In contrast, the orexigenic peptide, AgRP and ghrelin have the effect to decrease proinflammatory cytokines and increase body weight, food intake, and muscle mass.

The understandings of the pathological mechanism of anorexia and muscle metabolism in view of the crosstalk between brain and muscle will open the new way for the management of cachexia. In this review, we describe recent experimental and clinical studies that have examined the regulation of food intake and muscle wasting in cachexia.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

Contents

1. Introduction

Food intake is controlled by a complex network that depends on the central regulation of energy homeostasis. Signals that regulate food intake are ultimately integrated or coordinated by central mechanisms, particularly those in the hypothalamus. Many factors must be considered in the hypothalamic regulation of food intake, and the interactions between adiposity and the central neuropeptidergic cascade downstream of leptin are increasingly being studied.

Cancer cachexia is the main cause of death in approximately 20% of cancer patients (Inui and Meguid, 2003). Cachexia is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass (Evans et al., 2008). Cachexia is highly associated with anorexia, weakness, weight loss, muscle wasting, and inflammation. Those phenotypes of cachexia affect mortality, morbidity, and quality of life (Lainscak et al., 2008).

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