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Pathophysiological and therapeutic approaches of cachexia: A silent & progressive killer accompanied with cancer

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REVIEW ARTICLE

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ABSTRACT

Cancer cachexia syndrome is a frequent and important complication of cancer. It is the most devastating and life-threatening aspects of cancer which occur in 30% to 80% cancer patients. But unfortunately cachexia is often not observed at the time of diagnosis of cancer. While the initial medical intervention for cancer patients includes antitumor therapy and pain management, the consequences of cachexia and anorexia may be unnoticed, to the detriment of the patient's quality of life and his or her potential response to chemotherapy. The importance of a clearly defined therapeutic approach to treat cachexia is to improve the patient's overall wellbeing. It includes anorexia, loss of weight, weakness and impaired immune function. The cause of the syndrome still remains unclear. Many endocrinological and metabolic abnormalities are present, like hypermetabolism, glucose intolerance, increased proteolysis and lipolysis. Presented is a review of the Pathophysiology & pharmacological management of cachexia. Cancer cachexia arises from a complex interaction between the cancer and the host. This development includes cytokine production, release of proteolysis-inducing and lipid-mobilizing factors, and modification in intermediary metabolism. Main role in the development of cancer cachexia is played by cytokines: TNF, interleukin 1 and 6, interferon alfa and gamma.

INTRODUCTION

Epilepsy, Cachexia is a devastating syndrome which contributes to approximately 2 million deaths worldwide annually (Joanne et al., 2009). It is a major cause of weight loss and increased mortality and affects more than 5 million people in the United States. 'The shoulders, clavicles, chest and thighs melt away. This illness is fatal...'? Hippocrates (460C370 BC) (John et al., 2008). Hippocrates described a condition of wasting and progressive inanition among patients who were ill and dying. The Greek words Kakos, meaning "bad things," and Hexus, meaning "state of being," have led to the term cachexia to describe this syndrome (Aminah, 2003; Diana et al, 2012). Cachexia, a hypercatabolic state defined as accelerated loss of skeletal muscle in the condition of a chronic inflammatory response (Kotler, 2000). Many patients with chronic or end-stage diseases, such as infections, cancer, acquired immunodeficiency syndrome (AIDS), congestive heart failure, rheumatoid arthritis, tuberculosis, and Crohn's disease, develop cachexia. It also may develop in some elderly persons who have no apparent signs of disease. Cachexia literally means "bad condition" and is typically associated with a chronic wasting syndrome involving loss of both adipose tissue and lean body mass (Tisdale, 2003; Akio Inui, 2002). Cancer cachexia describes a syndrome of anorexia, progressive weight loss, and persistent erosion of host body cell mass in response to a cancerous tumor (Kern et al., 1998).

Pathophysiology of cachexia

Cachexia is a wasting condition that leads to weakness and a loss of weight, fat, and muscle. Other causes of weight loss include anorexia, Sarcopenia, and dehydration. Here we discuss current pathogenetic theories associated with common causes of Cachexia. The major cause appears to be cytokine excess (John et al., 2008). Other potential mediators include testosterone and insulin-like growth factor I deficiency, excess myostatin, and excess glucocorticoids. Several diseases can result in cachexia, each one by a slightly different mechanism (John et al., 2008).Weight loss and failure to gain weight usually in cancer patients are attributable to negative energy balance and altered metabolism. Energy balance is negative because of decreased intake, increased expenditure, or both. Altered carbohydrate metabolism is due to glucose uptake and lactate production by tumor, relative hypoinsulinism, and relative insulin resistance. Changes in protein metabolism

include preferential uptake of amino acids by the tumor, decreased synthesis of several host tissue proteins such as muscle tissue, and increase synthesis of other host proteins. Lipid metabolism is apparently less affected. These metabolic changes result in muscle wasting in adult cancer patients and growth failure in pediatric cancer patients (Diana et al, 2012). Host tissues are catabolized to meet the nutritional demands of the tumor which may leads to nutritional death. In some patients, factors causing reduced intake, for instance interference with normal gastrointestinal function may be apparent, but in many patients no clear cause of decreased intake can be discerned. In some patients, such as in a patient with fever, increased energy expenditure may be obvious, but in the majority of patients, increased expenditure escapes clinical detection (William, 1982). Clinically, cachexia manifests with excessive weight loss in the setting of ongoing disease, usually with inconsistent muscle wasting. Differentiation from other syndromes of weight loss is pivotal to early recognition and effective management of cachexia. Weight loss resulting from the syndrome of starvation occurs as a direct result of caloric deprivation. Starved persons usually lose more fat than muscle tissue. Sarcopenia is yet one more weight-loss syndrome that results primarily from muscle atrophy due to a variety of causes. A fourth, often ignored, cause of weight loss is dehydration, in which fluid loss accounts for the drop in measured weight (Thomas, 2002; Roubenoff et al., 2003). Even though numerous diseases are associated with cachexia, the underlying pathophysiological mechanisms are unclear (Thomas, 2002).

Factors implicated in production of cancer cachexia

Numerous cytokines, including tumor necrosis factor-a (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6), interferon gamma (IFN g), and leukemia-inhibitory factor (LIF), have been proposed to play a role in the etiology of cancer cachexia. These cytokines may be produced by tumor or host tissue and are characterized by the induction of anorexia and a decrease in the clearing enzyme lipoprotein lipase (Kayacan et al., 2006). The capability to inhibit lipoprotein lipase varies among the cytokines. Thus, while LIF is Twofold to 10-fold less potent than TNF-α, it is 100 times more potent than IL-6. Although, it is unlikely that a decrease in lipoprotein lipase alone could account for the fat cell depletion and wasting seen in cachexia, as in type 1 hyperlipidemia caused by an inherited deficiency in lipoprotein lipase, patients have normal fat stores and are not cachectic (Roubenoff et al., 2003; Noguchi et al. 1996; McNamara et al. 1992). TNF-α and IL-6 levels did not differ significantly between cachectics and non cachectics. However, significant correlations between IL-6, BMI (Body mass index) and TNF-α suggested that these cytokines act as co-factors in weight loss (Kayacan et al., 2006).

(a) Cytokines: A central player in the pathogenesis of cachexia

Cytokines are cell-associated proteins produced by inflammatory cells that function as paracrine intercellular mediators. Systemic inflammation mediated through cell injury or activation of the immune system generates an acute inflammatory response that causes excess cytokine elaboration. Cytokines play a major role in immunomodulation and have been implicated in the etiology of anorexia, weight loss, cognitive dysfunction, anemia, and frailty. Excessive elaboration of proinflammatory cytokines such as interleukin (IL) 1, IL-2, interferon, and tumor necrosis factor (TNF-α) is probably the most frequent cause of cachexia observed in acutely ill patients. Cytokines stimulate nuclear transcription factor B (NF-B), which results in decreased muscle protein synthesis. Cytokine activation is also responsible for the reduction of MyoD protein which is a transcription factor that modulates signaling pathways involved in muscle development. MyoD binding to myosin heavy chain IIb promoter region is essential for myosin expression in fast twitch muscles. TNF-α and interferon act synergistically to inhibit the activation of messenger RNA for myosin heavy chain synthesis. TNF-α and interferon are highly specific for stimulating the proteolysis of myosin heavy chains (Diana et al., 2012; Kayacan et al., 2006). Cytokines are also responsible for activation of ubiquitin-mediated proteolytic system which is the major system involved in disease-related hypercatabolism. Ubiquitin is a 76 amino acid, highly conserved polypeptide that targets specific proteins within skeletal muscle. Ubiquinated proteins are delivered into the hollow core of the proteasome by attachment to the 19S component. Consequent muscle proteolysis yields amino acids and oligopeptides that are consumed in hepatic synthesis of acute phase proteins such as C-reactive protein and serum amyloid peptide. The ubiquitin-proteasome system also indirectly modulates protein synthesis through degradation of inhibitory B protein (IKB) CNFB gene regulation. Furthermore, cytokines stimulate the release of cortisol and catecholamines from the adrenal gland (John Morley et al., 2008, Crown et al., 2002). Cortisol further propagates the activity of the ubiquitin-proteasome system and catecholamines which leads to an increase in resting metabolic rate. Cytokines induce lipolysis and -oxidation. Fat and liver lipoprotein lipase activity decreases, whereas LDL hepatocyte receptor activity increases. Subsequent increased VLDL synthesis and decreased lipoprotein lipase activity delays triacylglycerol clearance and result in hypertriglyceridemia. All these processes lead to negative energy balance and weight loss. Abundant evidence highlighting the major role of cytokines in cachexia supports ongoing efforts to use cytokine antagonism as a therapeutic option in cachexia (Crown et al., 2002; Kayacan et al., 2006).

(b) Other potential mediators of the cachexia syndrome

Testosterone: It is known that testosterone concentrations decline with aging and disease. Testosterone causes stimulation of myoblasts and increase in satellite cells, thereby promoting protein synthesis and efficient repair of damaged muscle.

Notably, Testosterone also inhibits the macrophage release of proinflammatory cytokines such as TNF-α, IL-1, and IL-6 and stimulates the production of IL-10, an anti-inflammatory cytokine. In addition to it low testosterone concentrations are associated with elevated circulating leptin concentrations. Leptin is an anorectic and lipolytic hormone produced by adipocytes. These changes probably account for age- and disease-related, weight loss, anorexia and cachexia in some hypogonadal men (Crown et al., 2002; Kayacan et al., 2006; John et al., 2008; Diana et al, 2012).

Insulin-like growth factor I: Circulating insulin-like growth factor I (IGF-I) concentrations are extremely sensitive to food intake, increasing markedly during an overnight fast. However, some evidences indicate that re-feeding adequately restores IGF values to baseline. Short-term nutritional status &dietary micronutrient composition also found to play an adjunctive role in determining IGF-1 concentrations. IGF-I is a potent anabolic agent, with therapeutic potential which stimulates muscle protein synthesis. IGF-I concentrations increase with growth hormone and testosterone administration, thus accounting for some of the effect of these hormones on muscle bulk and strength. Low IGF-I concentrations in malnourished humans suggest a role for IGF-I in the pathogenesis of cachexia (Crown et al., 2002; John et al., 2008).

Myostatin: Myostatin is a hormone produced in muscle that suppresses muscle growth by reducing myoblast proliferation. Genetic myostatin deletions produce double-muscled cows and muscle hypertrophy in mice. Recently, a double myostatin deletion was identified in a 1-year-old child with extreme muscle hypertrophy. It is observed that transgenic mice with the myostatin gene develop a cachexia-like syndrome with noticeable wasting. To date, similar human models have not been identified. In addition; myostatin assays in humans have technical limitations (John et al., 2008).

Adrenal hormones: Glucocorticoids suppress glucose and amino acid muscle uptake by inhibiting cellular transporters. Notably glucocorticoids also inhibit protein synthesis and promote gluconeogenesis, which contributes to steroid-induced myopathy and impaired glucose tolerance. Elevated glucocorticoids in cachectic patients may contribute to ongoing proteolysis and impaired protein synthesis (John et al., 2008, William, 1982).

Cachexia syndrome in cancer: Weight loss is a complaint of 15 to 40% of cancer patients and indicates poor prognosis. Cytokine activation in cancer has been well explained. Peripheral and central mechanisms have been implicated. Cytokine production in malignant disease increases corticotrophin releasing factor which is a potent anorectic agent, and, in concert with prostaglandins, suppresses the production of the orexigenic agent neuropeptide Y.

Cytokines also delay gastric emptying, lower serum albumin concentrations, and enhance lipolysis. Excessive lactate production from tumor cells exacerbates energy wasting by inducing the Cori Cycle in the liver and extra-hepatic tissues (William, 1982). Although anorexia often accompanies cachexia, the drop in caloric intake alone cannot account for the altered body-composition seen in cachexia, and, moreover, cachexia can occur even in the absence of anorexia. Norton et al. provided evidence for the parabiotic transfer of cachexia into rats, showing that cachexia must be mediated by some circulating factor. Animal models of the condition have suggested several factors which thought to play a role in the tissue wasting of cachexia.

They can be divided into two groups:

1. Products of host tissues, such as tumor necrosis factor-α (TNF-α), interleukins (IL)-1 andIL-6, interferon (IFN)-γ, and leukemia inhibitory factor (LIF) (Robert et al., 2011).
2. Tumor products which have a direct catabolic effect on host tissues, such as lipid mobilizing factor (LMF), which acts on adipose tissue, and Proteolysis-inducing factor (PIF) that acts on skeletal muscle.

Although evidence has been presented for circulatory levels of tumor catabolic products in humans, there are very few evidences for circulating cytokines. In several cases where serum levels of cytokines such as TNF-α are raised, these levels correlate with the stage of the disease, reflecting tumor size and metastasis. Notably, some cytokines, such as IL-6, may not be capable of producing cachexia alone. Thus, in a phase I study, patients received between 1 and 10 μg/kg/day of IL-6, but weight loss was not a common side effect; rather, toxicities consisted mainly of flu-like symptoms and fatigue. It is possible that tumor catabolic products and cytokines work together, with the former inducing total changes in cytokine production that then contribute to the overall development of cachexia (Tisdale, 2003). Evidently, the etiology of cachexia is multifactorial. However, emerging evidence suggests that cytokines play a central role in the pathogenesis of cachexia (John et al., 2008).

Treatment for cancer cachexia and its limitations

Weight loss is accompanied with psychological distress and a lower quality of life. In addition, patients with weight loss have a shorter survival time and a decreased response to therapy (Dewys, 1985). About half of all patients with cancer shows weight loss, but those with pancreatic cancer show it at the highest frequency; in the latter study, the investigators found that all patients at the time of diagnosis had lost weight (median, 14.2% of pre-illness stable weight), and this weight loss was progressive, reaching to a median of 24.5% just before death. Patients with more than 15%weight loss are likely to have considerable loss of total body protein, and at this level of lean function are markedly impaired. Thus, such patients need effective therapy if death from cachexia is not to occur (Roubenoff et al., 2003).

The best way to treat cancer cachexia is to cure the cancer, but unfortunately this remains a rare achievement among adults with advanced solid tumors. Hence, the next therapeutic preference is to increase

nutritional intake and to inhibit muscle and fat wasting by manipulating the metabolic milieu with a variety of pharmacological agents. The treatment should be focused on improving the quality of life (Miller, 1998; Reuben et al., 1988).

Nutritional support

Nutritional support improves quality of life but does not improve mortality rates associated with most cancers. The effects of caloric intake on tumor development and growth are still not understood (Miller, 1998). Therefore a clear benefit from nutritional support may be limited to a specific, small number of patients with severe malnutrition who may require surgery or may have an obstructing, but potentially therapy-responsive tumor. A novel approach is to supplement substances such as omega-3fatty acids which reduces IL-1 and TNF-α production and may improve the efficacy of nutritional support (Nitenberg et al., 2000). Nutritional support even in the form of total parenteral nutrition has failed to replete lean body mass. Even worse, a meta-analysis of the published trials on patients getting total parenteral nutrition when on chemotherapy showed a decreased survival, a poorer tumor response, and a significantly substantial increase in infectious complications. An improvement in appetite alone does not fully reverse the cachectic syndrome (William, 1982).

Glucocorticoids

Glucocorticoids are commonly used in the palliative setting for symptoms associated with cancer. There have been a number of randomized, placebo-controlled trials demonstrating the symptomatic effects of different types of corticosteroids. But most studies have shown an inadequate outcome of up to four weeks on symptoms such as appetite, food intake, sensation of well-being, and performance status (Roubenoff et al., 2003). Majority of studies have failed to show any beneficial effect of corticosteroids on body weight. Even prolonged treatment with corticosteroids may lead to weakness, delirium, osteoporosis, and immune suppression all of which are commonly present in advanced cancer patients (Kayacan et al., 2006).

Progestational Drugs

Megestrol acetate (MA) and medroxy-progesterone acetate (MPA) are synthetic, orally active derivatives of the naturally occurring hormone progesterone. In some clinical trials, these compounds have been found to improve appetite, caloric intake, and nutritional status (Roubenoff et al., 2003; Wai et al., 2012). Thus, patients with advanced malignant disease receiving medroxyprogesterone acetate (100 mg taken orally three times a day) showed a remarkable improvement in appetite, but this effect did not lead to weight gain or an improvement in performance status, energy levels, mood, or relief from pain. Results with the appetite stimulant megestrol acetate look more hopeful in terms of weight gain (McNamara et al., 1992). A number of clinical studies report an increase in appetite and weight gains of up to 6.8 kg over baseline values in 16% of patients treated. Though, body composition analysis, as determined by use of dual-energy X-ray absorptiometry and tritiated body water methodologies measured at the time of maximum weight gain, showed that the majority of patients weight from an increase in adipose tissue, while few gained weight due to an increase in body fluid. A prominent increase in lean body mass was not reported. Such body composition changes are similar to those also observed in patients receiving total parenteral nutrition (McNamara et al., 1992). These both drugs can induce thromboembolic phenomena, breakthrough uterine bleeding, peripheral edema, hyperglycemia, hypertension, adrenal suppression, and adrenalin sufficiency (Crown et al., 2002; Kayacan et al., 2006).

Cyproheptadine and other antiserotonergic drugs

Cyproheptadine is an antiserotonergic drug with antihistaminic properties also shown to have an appetite-stimulant effect in a number of human conditions (Kayacan et al., 2006). Number of clinical studies reveals a weight enhancing effect for the Cyproheptadine. In addition, data from some basic research suggests that cyproheptadine may be helpful in patients with cancer anorexia/cachexia. Since, the researchers performed a randomized, placebo-controlled, double-blinded clinical trial using cyproheptadine, 8 mg orally three times a day in 295 patients with advanced malignant disease. Patients receiving cyproheptadine had less nausea (P = 0.02), less emesis (P = 0.11), more sedation (P = 0.07), and more dizziness (P = 0.01) than placebo patients. Patients' appetites appeared to be mildly enhanced by cyproheptadine. Unfortunately, cyproheptadine did not significantly reduce progressive weight loss in these patients with advanced malignant disease; patients assigned to cyproheptadine lost an average of 4.5 pounds per month compared to 4.9 pounds per month for patients assigned to a placebo (P = 0.72) (Argiles et al., 2001; Carl et al., 2006; Argiles et al., 2013).

Cannabinoids

Appetite stimulation and body weight gain are well-recognized effects of the use of cannabinoids. Dronabinolis the synthetic, oral form of tetrahydro cannabinol (THC), which is the active ingredient responsible for above said effect (Crown et al., 2002; Kayacan et al., 2006). Dronabinol and Marinol (in the United States) and Nabilone (in Canada) have been used as antiemetics in cancer, with several studies indicating their efficiency in treating chemotherapy-induced nausea and vomiting (Crown et al., 2002). It has been shown that almost 20 percent of the cancer patients receiving chemotherapy along with dronabinol as antiemetic experienced side effects, such as euphoria, dizziness, somnolence, and confusion resulting in a dose reduction or probably withdrawal of the treatment (Miller, 1998). Further randomized, controlled trials are essential to determine the efficacy and usefulness of cannabinoids in cancer cachexia.

Prokinetic agents

Many patients with advanced cancer experience delayed gastric emptying and gastric stasis. Autonomic failure with reduced gastrointestinal motility is a known complication of cancer cachexia which leads to anorexia, chronic nausea, early satiety, and constipation result in reduced caloric intake. The prokinetic agent, metoclopramide, 10 mg orally before meals and at bedtimes, may relieve anorexia and early satiety with nominal side effects. It has been the most extensively used drug in patients with cancer for the prevention and treatment of chemotherapy-induced emesis but it did not show any favorable effects in treatment of cachexia (Loprinzi et al., 1994; Mateen, 2006)

Anabolic steroids

Anabolic steroids increase muscle mass in non cancer patients, and this has led to their abuse for athletic advantage. In large, randomized, controlled trial megestrol acetate compared with dexamethasone versus fluoxymesterone for the treatment of cancer cachexia, it is found that fluoxymesterone was clearly inferior (Miller, 1998; Loprinzi et al., 1994; Mateen, 2006).

DISCUSSION

Findings confirmed that cancer cachexia has severe consequences on patients and their families, extending beyond physical problems into psychological, social and emotional issues. In recent years, cancer cachexia has been estimated as a result of major central nervous system (CNS) and metabolic abnormalities. These are due to a combination of tumor by-products and host cytokine release rather than a simple increase in energy consumption by the tumor and starvation on the part of the patient. In cachexia the resulting malnutrition and loss of lean body mass deteriorates the quality of life for the affected individual and also affects recovery by decreasing tolerance to therapy and increasing postsurgical complications. Therefore, it is suggested to think of the clinical features as array of severity that ranges from mild anorexia to severe cachexia and to concentrate on early therapeutic intervention. As discussed above, attempts at drug therapy for cachexia with a variety of agents have shown limited success. The most commonly used agent, megestrol acetate, has shown some potential in reversing weight loss though this may be due to the increase in fat mass and subtle water retention rather than the preservation of lean body mass. Presently, several new and exciting drugs are reaching the stage of clinical trials, including melanocortinant agonists, growth hormone secretagogues (synthetic agonists of ghrelin, a newly-identified orexigenic peptide), and cytokine antagonists or inhibitors. These agents offers the possibilities of combined drug therapy that may simultaneously address the different aspects of cancer cachexia and lead to more precise and targeted pharmacological interventions. Caregivers often note that when conflict occurs between themselves and the individual for whom they are caring, it often occurs over the issue of eating. These caregivers report that they find it difficult to cope with the patient who continually loses weight and strength and yet persistently refuses adequate food intake. Cachexia is an important cause of mortality in cancer patients, accounting directly for between 10% and 22% of all cancer deaths. Now it is clear that cachexia is not due only to a nutrient deficit or to tumor/host competition for essential nutrients, but to complex metabolic changes in tissues arising from tumor catabolic factors, which may be enhanced by proinflammatory cytokines.

CONCLUSION

Knowledge of the fundamental mechanisms of development of cachexia has led to improved treatments, which hopefully will be shown to extend lifespan, as well as improve the quality of life of the patient. It is expected that further developments will concentrate on inhibitors of protein degradation together with stimulation of protein synthesis. Inhibition of the increased energy demands will also restore adipose tissue reserves. Considering that cachexia is common in those cancers for which treatment is currently limited, this could prove to be of great clinical benefit. Improvements in the therapy of cancer might well negate the necessity for anticachexia therapy.

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