# CACHEXIA AND MUSCLE WASTING IN CANCER PATIENTS

## INDEX

## DEFINITION:

***"….the shoulders, clavicles, chest and thighs melt away. This illness is fatal…"***
***—Hippocrates (460–370 BC)***

Cachexia is amultifactorial process of skeletal muscle and adipose tissue atrophy resulting in progressive weight loss. It is associated with poor quality of life, poor physical function, and poor prognosis in cancer patients. It involves multiple pathways: procachectic and proinflammatory signals from tumour cells, systemic inflammation in the host, and widespread metabolic changes (increased resting energy expenditure and alterations in metabolism of protein, fat, and carbohydrate). Whether it is primarily driven by the tumour or as a result of the host response to the tumour has yet to be fully elucidated. Cachexia is compounded by anorexia and the relationship between these two entities has not been clarified fully. Inconsistencies in the definition of cachexia have limited the epidemiological characterisation of the condition and there has been slow progress in identifying therapeutic agents and trialling themin the clinical setting. Understanding the complex interplay of tumour and host factors will uncover new therapeutic targets.

The etymology of the word cachexia points to its association with poor prognosis: it is derived from the Greek kakos and hexia—"bad condition" and has long been recognised as a key sign in many cancers. It is a multifactorial condition which comprises skeletal muscle and adipose tissue loss which may be compounded by anorexia, a dysregulated metabolic state with increased basal energy expenditure and is resistant to conventional nutritional support.

The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance, and increased muscle protein breakdown are frequently associated with cachexia.

The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance, and increased muscle protein breakdown are frequently associated with cachexia [6]. However, there is no clear consensus definition of this common problem in cancer patients leading to a poor understanding of the aetiology of the condition. Earlier definitions of cachexia described "a wasting syndrome involving loss of muscle and fat directly caused by tumour factors, or indirectly caused by an aberrant host response to tumour presence" [7], however more recent definitions have downplayed the importance of fat loss and describe cachexia as "a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass" [6], thus highlighting the unique consequences of muscle wasting—the hallmark of cachexia. Without an established definition, future studies in this area will be hampered. A recent consensus definition has been proposed to include further factors to diagnose the cachexia syndrome such as involuntary weight loss, decreased muscle mass, anorexia, and biochemical alterations (*C*-Reactive Protein (CRP), albumin, haemoglobin Cancer-induced cachexia (CIC) is experienced by up to 80% of patients with advanced stage cancer, particularly those with gastrointestinal, pancreatic, thoracic and head and neck

malignancies.i CIC has been implicated in up to 20% of cancer-related deaths.ii,iii The definition of cachexia appears to be well-defined among the scientific community, however the term is liberally employed in clinical oncology practice. The 2006 Cachexia Consensus Conference, established cachexia as "a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass".iv Many oncologists confuse cancer-induced cachexia with simple starvation, or physiologic processes such as sarcopenia (age-related loss of muscle mass).v,vi

**Anorexia** loss of appetite and resulting reduced caloric intake. **Cachexia** – involuntary weight loss of more than 10% of pre-morbid weight, associated with loss of muscle and visceral protein and lipolysis (the breakdown of fat stored in fat cells). Cachexia may not correlate with anorexia. The anorexia-cachexia syndrome is usually defined in terms of primary or secondary causes. Primary cause is related to changes (metabolic and neuroendocrine) directly associated with underlying disease and an ongoing inflammatory state. Secondary causes are aggravating factors (fatigue, pain, dyspnea, infection, etc) that contribute to weight loss.(1-3, 6-13)

## DIAGNOSIS OF CACHEXIA:

**Diagnostic criteria for cachexia syndrome**
Weight loss of at least 5% in 12 months or less (or BMI <20 kg/m2)
**AND 3 of 5 From below:**
Decreased muscle strength
Fatigue
Anorexia
Low fat-free mass index
Abnormal biochemistry: Increased inflammatory markers (CRP, IL-6), Anaemia (Hb < 12 g/dL), Low serum albumin (<3.2 g/dL)

**Diagnostic criteria for cachexia**
Unintentional weight loss (≥50%)
BMI
<20 in those aged _65 y
<22 in those aged _65 y
Albumin < 35 g/L (3.5 g/dL)
Low fat-free mass (lowest 10%)
Evidence of cytokine excess (eg, elevated C-reactive protein)

## BURDEN OF DISEASE:

About half of all cancer patients show a syndrome of cachexia, characterized by anorexia and loss of adipose tissue and skeletal muscle mass. Cachexia can have a profound impact on quality of life, symptom burden, and a patient's sense of dignity. It is a very serious complication, as

weight loss during cancer treatment is associated with more chemotherapy-related side effects, fewer completed cycles of chemotherapy, and decreased survival rates.

Cachexia causes weight loss and increased mortality. It affects more than 5 million persons in the United States. Other causes of weight loss include anorexia, sarcopenia, and dehydration. Cachexia (Gr. Kachexi a; kako's bad; "e xis condition) is a major cause of weight loss and increased mortality and affects more than 5 million people in the United States (Table 1) (1). Clinically, cachexia manifests with excessive weight loss in the setting of ongoing disease, usually with disproportionate muscle wasting (Table 2).

Differentiation from other syndromes of weight loss is pivotal to prompt recognition and effective management of cachexia. Weight loss resulting from the syndrome of starvation occurs as a direct result of caloric deprivation. Starved persons generally lose more fat than muscle tissue. Sarcopenia is yet another weight-loss syndrome that results primarily from muscle atrophy due to a variety of causes.Afourth, often neglected, cause of weight loss is dehydration, in which fluid loss accounts for the reduction in measured weight

**TABLE 1**
The number of persons in the United States with cachexia

| **Disease** | **No. with disease** | **Cachexia %** |
|---|---|---|
| AIDS*2* | 900 000 | 35 |
| Cancer | 1 368 000 | 30 |
| COPD | 16 000 000 | 20 |
| **Kidney failure** | **375 000** | **40** |
| Rheumatoid arthritis | 2 100 000 | 10 |
| Heart failure | 4 800 000 | 20 |
| Nursing home | 1 600 000 | 20 |

The prevalence of cachexia is thought to be up to 80% of upper gastrointestinal cancer patients and 60% of lung cancer patients at the time of diagnosis [9]. There are no clear figures for the estimated prevalence within specific cancer cohorts. When the electronic medical records of over 8500 patients with a wide variety of malignancies were analysed for the prevalence of cachexia amongst the cohort, the proportion varied according to which standard definition was used: 2.4% using the World Health Organisation's International Classification of Diseases (ICD) cachexia diagnostic code; 5.5% for the ICD diagnosis of cachexia, anorexia, abnormal weight, and feeding difficulties; 6.4% were prescribedmegestrol acetate, oxandrolone, somatropin, or dronabinol; 14.7% had >5% weight loss [10]. Despite methodological flaws, there was an interesting lack of overlap between the different criteria pointing to the underdiagnosis of cachexia in clinical practice.

## PATHOPHYSIOLOGY OF CACHEXIA:

The major cause appears to be cytokine excess. Other potential mediators include testosterone and insulin-like growth factor I deficiency, excess myostatin, and excess glucocorticoids.

Numerous cytokines have been postulated to play a role in the etiology of cancer cachexia. Cytokines can elicit effects that mimic leptin signaling and suppress orexigenic ghrelin and neuropeptide Y (NPY) signaling, inducing sustained anorexia and cachexia not accompanied by the usual compensatory response. Furthermore, cytokines have been implicated in the induction of cancer-related muscle wasting. Cytokine-induced skeletal muscle wasting is probably a multifactorial process, which involves a protein synthesis inhibition, an increase in protein degradation, or a combination of both. The best treatment of the cachectic syndrome is a multifactorial approach

### Hormones and mediators

**Leptin** is a protein hormone that sends afferent signals from the periphery to the brain that regulates adipose tissue mass [1–3]. The level of leptin is positively correlated with body fat mass, and dynamic changes in plasma leptin concentrations in either direction can activate the efferent energy regulation pathways [1, 4]. Leptin reduces appetite and increases energy expenditure and evidently elicits these effects via the central nervous system [1, 4]. This is achieved by hypothalamic neuropeptides downstream of leptin that regulate food intake and energy expenditure. Starvation or a loss of body fat can lead to a decrease in leptin, which in turn leads to a state of positive energy balance; conversely, food intake exceeds energy expenditure. This compensatory response is mediated by the increased production of ghrelin, neuropeptide Y (NPY), and other appetite-stimulating neuropeptides, and decreased activity of anorexigenic neuropeptides such as corticotropin- releasing factor (CRF) and melanocortin (Fig. 1a).

Thus, if a disease process such as cancer was to produce factors that induce or mimic the hypothalamic effect of excess negative feedback signaling from leptin, the expected outcome would be sustained anorexia (lack of appetite) and cachexia (muscle wasting and uncontrolled weight loss), without the usual compensatory response [5]. In fact, in tumor-bearing states, cachectic factors such as cytokines can elicit effects on energy homeostasis that mimic leptin and suppress orexigenic ghrelin and NPY signaling. Consequently, the increases and decreases in hypothalamic actions caused by these mediators induce anorexia and unopposed weight loss (Fig. 1b).

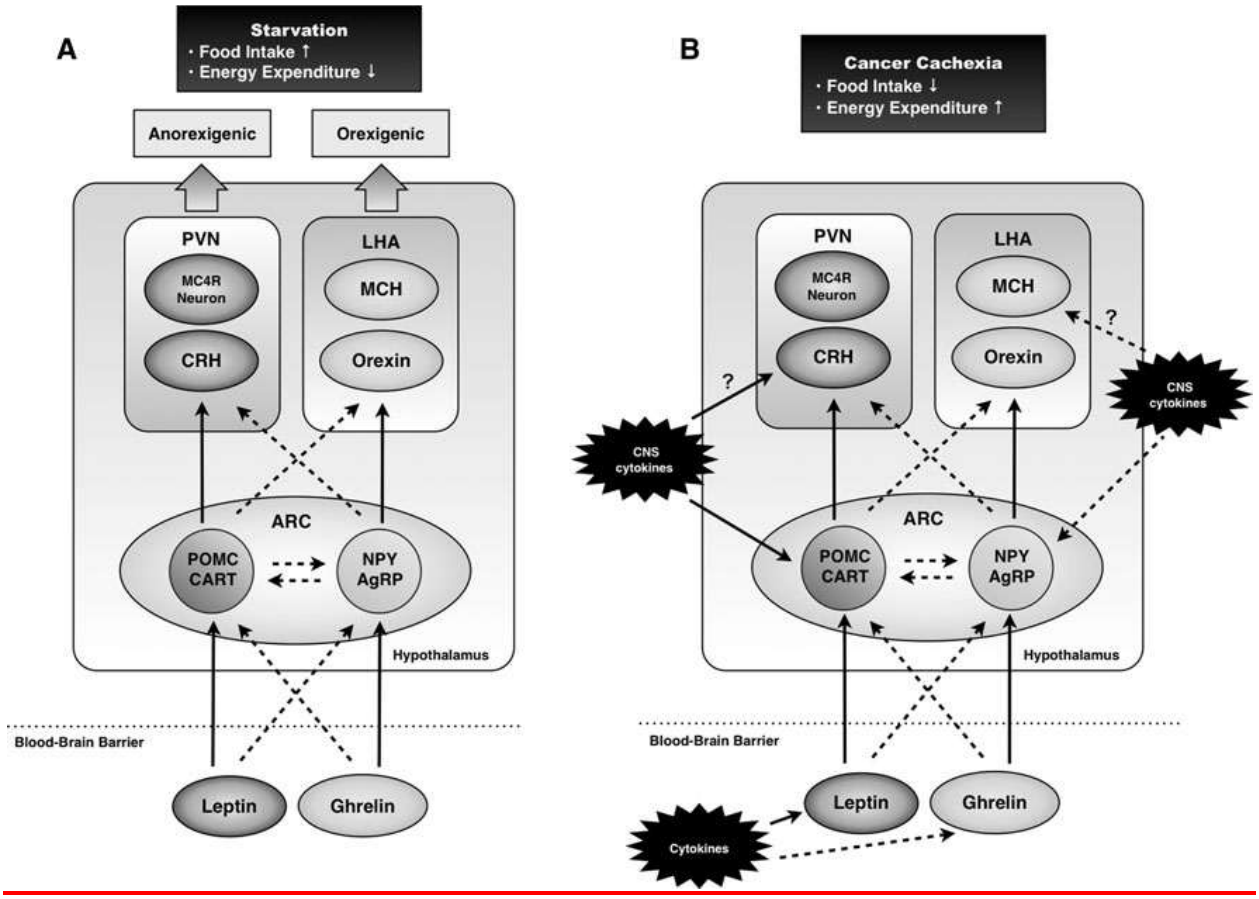



Fig. 1 A simplified model of the hypothalamic neuropeptide circuitry in response to starvation (a) and cancer cachexia (b). Full line arrows indicate the activation of the process, and broken line arrows indicate the inhibition of the process. Under normal conditions, energy intake is determined by the hypothalamic integration of peripheral signals conveying inputs on adiposity status, digestive processes, and metabolic profile. Some of these signals such as adipocyte-derived leptin inhibit energy intake, while other signals such as stomach-derived ghrelin stimulate energy intake. In the hypothalamus, the arcuate nucleus (ARC) receives information from the periphery and integrates these inputs to modulate food intake via second-order neurons. According to the information conveyed to the brain, peripheral signals may differentially activate or inhibit POMC/ CART and NPY/AgRP neurons. When an energy deficit (e.g., starvation) is signaled, orexigenic NPY/AgRP neurons are activated and anorexigenic POMC/CART neurons are inhibited, resulting in increased energy intake. When an energy excess is signaled, NPY/AgRP neurons are inhibited and POMC/CART neurons are activated. During cancer, cachectic factors such as cytokines elicit effects on energy homeostasis that mimic leptin in some respects and suppress orexigenic Ghrelin-NPY/AgRP signaling. Increased brain cytokine expression disrupts hypothalamic neurochemistry, particularly in the ARC where cytokines activate POMC/CART neurons, while inactivate NPY/AgRP neuron s. The anorexia and unopposed weight loss in cachexia could be accomplished through persistent inhibition of the

NPY orexigenic network and stimulation of anorexigenic neuropeptides, although the hypothalamic pathways participating in this response remain to be determined. AgRP Agouti-related peptide, MCH melanin-concentrating hormone, CART cocaine- and amphetamine-related transcript, NPY neuropeptide Y, POMC proopiomelanocortin, CRH corticotropin-releasing hormone, MC4R melanocortin-4 receptor, PVN paraventricular nucleus. LHA lateral hypothalamic area.

**Testosterone**

Testosterone concentrations decline with aging and disease (20 –22). Testosterone stimulates myoblasts and increases satellite cells, thereby promoting protein synthesis and efficient repair of damaged muscle (23). Testosterone also inhibits the macrophage release of proinflammatory cytokines such as TNF-_, IL-1_, and IL-6 (24, 25) and stimulates the production of IL-10, an antiinflammatory cytokine (26). Notably, low testosterone concentrations are associated with elevated circulating leptin concentrations. Leptin is an anorectic and lipolytic hormone produced by adipocytes (27). These changes probably account for age- and disease-related anorexia, weight loss, and cachexia in some hypogonadal men (28 –30).

**Adrenal hormones**

Glucocorticoids suppress glucose and amino acid muscle uptake by inhibiting cellular transporters (46, 47). Glucocorticoids have a permissive effect on the up-regulation of messengerRNA and the subsequent synthesis of components of the ubiquitinproteasome system in muscle (13, 48). 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.

**Serotonin (5-HT)** may also play a role in the development of cancer-induced anorexia. This is because increased levels of plasma and brain tryptophan, the precursor of 5-HT, and interleukin (IL)-1 may underlie the increased serotonergic activity seen in the cancer cachexia. In addition, cisplatin-induced anorexia has become problematic in clinical settings. Cisplatin is a widely used and effective anti-cancer chemotherapy drug, however, the undesirable gastrointestinal side effects associated with it, such as nausea, vomiting, and anorexia, markedly decrease patients' quality of life, rendering continuation of chemotherapy difficult [6]. Cisplatin-induced gastrointestinal tract disorders are thought to be due to the release of large amounts of 5-HT from enterochromaffin cells, which then bind to 5-HT receptors [6]. 5-HT activates various serotonin receptor subtypes in the gastrointestinal tract and ganglia, exerting a range of biological and physiological effects [6]. It has been reported that a significant increase in 5-HT concentrations in the hypothalamus of cisplatintreated rats [7].

Accumulated findings suggest that serotonin 2C (5-HT2C) receptor subtypes are involved in appetite regulation [8, 9]. The 5-HT2C receptor subtype is expressed in proopiomelanocortin neurons in the hypothalamus, which is the major site of its anorexigenic action [6]. In the present clinical setting, nausea and vomiting can be controlled by administering 5-HT3 receptor antagonists together with anticancer agents [6]. However, 5-HT3 receptor antagonists may not be sufficiently controlled in cisplatininduced anorexia [6]. Recent studies have reported that cisplatin-induced anorexia is mediated through reduced gastric and hypothalamic ghrelin

secretion, and peripheral 5-HT2B and cerebral 5-HT2C receptor activation are responsible for the phenomenon [6, 10, 11]. Facilitating the gastric and hypothalamic ghrelin secretion through 5-HT2C receptor inhibition can be a useful therapeutic approach for cisplatin-induced anorexia. been great progress in understanding the underlying biological mechanisms of cachexia, health care providers must also recognize the psychosocial and biomedical impact cachexia can have.

## CYTOKINES: A CENTRAL PLAYER IN THE PATHOGENESIS OF CACHEXIA

Cytokines are protein molecules released by lymphocytes and/or monocyte macrophages [5]. They are released into the circulation and transported to the brain through the blood–brain barrier (BBB) and circumventricular organs (i.e., 'leaky' areas in the BBB) [12–17]. Peripheral cytokines may influence the brain via neural pathways or second messengers such as nitric oxide (NO) and prostanoids [5]. Cytokines are also produced by neurons and glial cells within the brain, partly in response to peripheral cytokines [12–17]. Although the site of cytokine synthesis within the brain is dependent on the nature of the stimulus, systemic disease seems to predominantly influence expression in the hypothalamus, the area with the highest densities of receptors [16]. Numerous cytokines, including tumor necrosis factor alpha (TNF-a), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon-gamma (IFN-c), have been postulated to play a role in the etiology of cancer cachexia [12, 13, 18–21]. It is not certain whether the cytokine production is primarily from tumour or host inflammatory cells. It has been hypothesised that either tumour cell production of proinflammatory cytokines or the host inflammatory cell response to tumour cells is the source of the acute phase protein response (APPR) seen in many malignancies and in cachexia [22]. High serum levels of TNF-a, IL-6, and IL-1 have been found in some cancer patients, and the levels of these cytokines seem to correlate with the progression of some tumors [23–25]. Chronic administration of these cytokines, either alone or in combination, is capable of reducing food intake and inducing cancer cachexia [18, 23–26]. The role of TNF-a in mediating cancer cachexia is supported by evidence that intraperitoneal injection of a soluble recombinant human TNF-receptor antagonist improved anorexia in tumor-bearing animals [27]. In humans, IL-1 appears to play a significant role in mediating cachexia, as megestrol acetate has been shown to exert its effects via reduced expression of IL-1 by mononuclear cells beyond its influence on hypothalamic NPY concentrations, which shows orexigenic effect.

TNF-a, IL-1, IL-6, and IFN-c have been implicated in the induction of cancer-related muscle wasting [30]. There is growing evidence that the accelerated muscle proteolysis seen during malignant tumor growth is mediated by the activation of the non-lysosomal adenosine triphosphatedependent (ATP-dependent) ubiquitin proteasome pathway [31, 32]. In addition, inflammatory cytokines influence the expression of functionally relevant enzymes in cardiac cachexia [30]. It has been demonstrated that TNF-a, IFN-c, and IL-1b are potent activators of inducible nitric oxide synthase (iNOS) expression [30], which in turn produces toxic levels of NO high enough to inhibit the key enzymes of oxidative phosphorylation [30]. It has also been shown in vitro that NO is able to impair the contractile performance of skeletal muscle [33]. C-reactive protein

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 triggers 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 (4–8). Excessive elaboration of proinflammatory cytokines such as interleukin (IL) 1, IL-2, interferon _, and tumor necrosis factor_ (TNF-_) is probably the most common cause of cachexia observed in acutely ill patients (9) (**Figure 1**). Cytokines activate nuclear transcription factor _B (NF-_B), which results in decreased muscle protein synthesis (10, 11). Cytokine activation is also responsible for the reduction of MyoD protein, a transcription factor that modulates signaling pathways involved in muscle development (12).MyoDbinding to myosin heavy chain IIb promoter region is necessary for myosin expression in fast twitch muscles (11). TNF-_ and interferon _ act synergistically to inhibit the activation of messengerRNAfor myosin heavy chain synthesis.

TNF-_ and interferon _ are highly specific for stimulating the proteolysis of myosin heavy chains (12). Cytokines also activate the ubiquitin-mediated proteolytic system which, is the major system involved in disease-related hypercatabolism (13). 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. Subsequent muscle proteolysis yields amino acids and oligopeptides that are consumed in hepatic synthesis of acute phase proteins such as C-reactive protein and serum amy loid peptide. The ubiquitin-proteasome system also indirectly modulates protein synthesis through degradation of inhibitory _ B protein (IKB)–NF_B gene regulation. Additionally, cytokines stimulate the release of cortisol and catecholamines from the adrenal gland (14, 15). Cortisol further propagates the activity of the ubiquitin-proteasome system, and catecholamines lead to an increase in resting metabolic rate.

Cytokines induce lipolysis and _-oxidation (16). Fat and liver lipoprotein lipase activity decrease, whereas LDL hepatocyte receptor activity increase (17, 18). Subsequent increased VLDL synthesis and decreased lipoprotein lipase activity hinder triacylglycerol clearance and result in hypertriglyceridemia (19). All these processes result in negative energy balance and weight loss (9). Notably, sickness behavior is also attributed to peripheral and central cytokine-mediated effects on the nervous system. Sickness behavior produces symptoms such as listlessness, malaise, and anhedonia, which further compromise energy intake. Abundant evidence highlighting the prominent role of cytokines in cachexia supports ongoing efforts to use cytokine antagonism as a therapeutic option in cachexia (Table 3).

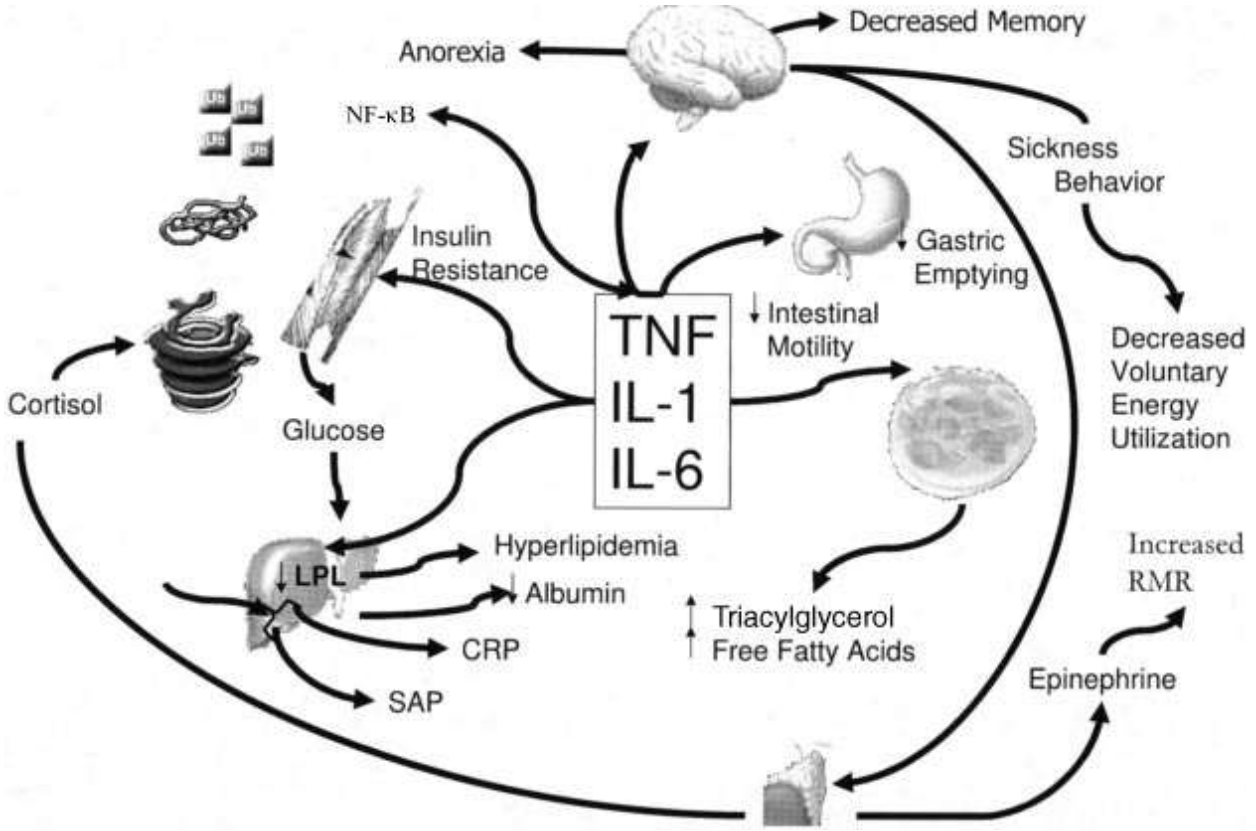



**FIGURE 1.** The pathophysiologic role of cytokines in the production of cachexia. TNF, tumor necrosis factor; IL-1, interleukin 1; IL-6, interleukin 6; RMR, resting metabolic rate; LPL, lipoprotein lipase; CRP, C-reactive protein; SAP, serum amyloid protein.

***TNF-alpha***

TNF-alpha/cachectin, a 17kDa protein consisting of 157 amino acids, is produced by stimulated reticuloendothelial cells, principally macrophages and monocytes102. The receptors for TNF have been identified in nearly all tissues103. The half-life is 14-18 min in humans and 10 min in mice104. TNF is a well-documented growth factor for many normal cells, stimulating cellular growth and differentiation105, and inducing production of a variety of compounds, including PGE2, collagenase, platelet activating factor, IL-1 and IL-6106. TNF also enhances angiogenesis107. A single injection of TNF alpha can cause a characteristic weight loss due to a reduction in food and water intake and a decreased carcass water content108.

However, when rats received chronic (5- day) infusions of rH-TNF, profound anorexia and fluid retention, but not accelerated nitrogen losses, were observed109. Darling and Norton110 reported that a continuous i.v. infusion of TNF, rather than an intermittent bolus i.v. resulted in a decreased food intake and a decreased nitrogen balance. After 4 days of treatment, rats treated with intermittent bolus doses of TNF developed tolerance. The TNF decreases LPL activity and increases hepatic lipogenesis111,112. Cellstransfected with the TNF gene inserted near an active promotor were injected into nude mice, which produced a sustained release of TNF and resulted in a severe wasting of host body fat and lean tissue mass, progressive cachexia and eventual death113,114,115. Active TNF genes were demonstrated in the tumor and lymphoid tissue of

MCA sarcoma bearing mice116 and in human colorectal tumors117. However, only a few papers have documented increased serum TNF in tumor-bearing patients118,119. No correlation between severity of cachexia and TNF concentrations was found120,121.

***IL-6***

IL-6, a 26kDa protein, is perhaps the most extreme example of a pleiotropic cytokine. It has a broad range of activities on different cells and was originally found as a growth factor for transformed B-cells122. Some of its functions include stimulation and differentiation of B-cells (BSF-2)123, supporting hybridoma and plasmacytoma cell growth (HGF/PGF), and stimulating synthesis of host response proteins by liver following exposure to toxic materials or injury (HSF) 124. IL-6 is secreted by monocytes, fibroblasts, keratinocytes, endothelial cells,and Bcells. A specific, high affinity receptor for IL-6 is distributed on many different cells throughout the organism. Is IL-6 the circulating message that induces anorexia125 and the hepatic acute phase reactants? Elevated serum levels of IL-6 were demonstrated in Balb/c x DBA/2(CD) mice with colon 26 carcinoma126. The effects of IL-6 in vivo were assessed by inoculating nude mice with Chinese hamster ovarian cells that had been transfected with the murine IL-6. Only those inoculated with the transfected IL-6 gene demonstrated a number of paraneoplastic syndromes including hypercalcemia, cachexia, leukocytosis, and thrombocytosis127.

Both the injection of IL-6 in mice and the culture of 3T3-L1 adipocytes in the presence of IL-6 reduced tissue and heparin-releasable LPL activity in a dose-dependent ma nner128. IL-6 was also demonstrated immunohistochemically in human tumor specimens129. Furthermore, some of the alterations were reversed by neutralizing anti bodies to IL-6 (eg. the hypercalcemia associated with a human squamous cell carcinoma130, the deplete on of carcass weight and epididymal fat, hypoglycemia, and the increase in serum amyloid P126).

**C-reactive protein (CRP)** is the most common method used to assess the magnitude of the systemic inflammatory response [36]. The modified Glasgow prognostic score combines CRP and plasma albumin concentrations to create a simple scoring system that serves as a prognostic factor that is independent of stage and treatment and that predicts survival [40, 41] (Table 1).Raised CRP concentrations at the time of admission to hospital is indicative of an increased risk for all-cause mortality; there is a 22.8-fold increase in cancer mortality in patients with highly elevated CRP concentrations ([80 mg/L) [42]. It has been shown that patients with inoperable non-small cell lung cancer had at least 5 % weight loss and almost 80 % an elevated CRP levels [43]. In patients without weight loss, those who displayed evidence of a systemic inflammatory response reported more fatigue (P\0.05) [43]. In another study of patients with gastroesophageal cancer, the rate of weight loss was also correlated with elevated CRP serum concentrations [44].

**Negative nitrogen balance**

In adults, muscle mass remains fairly constant in the absence of stimuli (e.g., exercise) and thus protein synthesis and degradation generally remain in balance [45]. However, in cachexia, muscle atrophy occurs, which results from a decrease in protein synthesis, an increase in protein

degradation, or a combination of both [45]. In recent years, it has become evident that specific regulating molecules are upregulated (e.g., members of the ubiquitin– proteasome system, myostatin, and apoptosis inducing factors), whereas other factors (e.g., insulin-like growth factor 1) are down-regulated in cachexia muscle wasting [30]. A major barrier to the effective management of skeletal muscle wasting is the inadequate understanding of its underlying biological mechanisms [30]. The most evident metabolic explanation for muscle decline is an imbalance between protein catabolism and anabolism [30]. In addition to an increase in catabolism, a reduction in anabolism has been shown to occur in cancer cachexia [30].

Skeletal muscle wasting in cancer cachexia can be mediated by multiple factors derived from tumor and host cells [46]. At least four major proteolytic pathways (**lysosomal, Ca2?-dependent, caspase-dependent, and ubiquitin–proteasome- dependent)** operate in skeletal muscle and may be altered during muscle cachexia [30]. Aside from these four distinct pathways, the autophagic/lysosomal pathway must also be considered [30]. In this pathway, portions of the cytoplasm and cell organelles are sequestered into autophagosomes, which subsequently fuse with lysosomes, where the proteins are digested [47].

**Myostatin**

Myostatin is an extracellular cytokine that is mostly expressed in skeletal muscles and is known to play a crucial role in the negative regulation of muscle mass [56]. Upon binding to the activin type IIB receptor, myostatin can initiate several different signaling cascades, resulting in decreased muscle growth and differentiation [56]. Muscle size is regulated via a complex interplay of myostatin signaling with the IGF-1/PI3K/Akt pathway, which is responsible for increased protein synthesis in muscle [56]. Therefore, the regulation of muscle weight is a process in which myostatin plays a central role, but the mechanism of its action and the role of the signaling cascades involved are not fully understood [56]. Myostatin upregulation was observed in the pathogenesis of muscle wasting during cancer cachexia [56]. Data are available that demonstrate a beneficial effect of myostatin inhibition in cancer cachexia [57], but conflicting study results have also been reported [58].

Myostatin is a hormone produced in muscle that suppresses muscle growth by inhibiting myoblast proliferation (40). Genetic myostatin deletions produce double-muscled cows and muscle hypertrophy in mice (41– 43). Recently, a double myostatin deletion was identified in a 1-y-old child with extreme muscle hypertrophy (44). Transgenic mice with the myostatin gene develop a cachexia-like syndrome that manifests with severe wasting (45). Similar human models have not been identified. Additionally, myostatin assays in humans have technical limitations.

**Insulin-like growth factor-1**

One of the main positive regulators of muscle growth is IGF-1 [56]. Under normal conditions, IGF-1 signaling seems to be dominant and blocks the myostatin pathway [61]. However, an inhibition of IGF-1 can occur when myostatin is overexpressed [62, 63]. IGF-1 can prevent TGF-a family-mediated apoptosis [64], and it was shown that in the absence of IGF-1, the level of apoptosis in C2C12 cells treated with myostatin increased [56]. The mechanism by which IGF-1

regulates myostatin signaling includes the inhibition of transcription factors responsible for the induction of atrogenes via phosphorylation through the PI3K/Akt pathway [56].

Circulating Insulin-like growth factor I (IGF-I) concentrations are highly sensitive to food intake, increasing markedly during an overnight fast. However, limited evidence indicates that refeeding adequately restores IGF values to baseline. Short-term nutritional status, dietary micronutrient composition, and essential amino acid concentrations also seem to play an adjunctive role in determining IGF-1 concentrations (31, 32). IGF-I increases muscle protein synthesis. IGF-I concentrations increase with growth hormone and testosterone administration, thereby accounting for some of the effect of these hormones on muscle bulk and strength (33, 34). Stem cells that express the muscle isoform of IGF-I prevent sarcopenia in old rodents (35, 36). Low IGF-I concentrations in malnourished humans suggest a role for IGF-I in the pathogenesis of cachexia (37–39).

Another factor that may contribute to decreased anabolism is **angiotensin II [**30]. In an animal model of continuously administered angiotensin II, markedly reduced plasma IGF-1 levels occurred [67]. Compared with a sham treatment, angiotensin II-infused hypertensive rats lost 18–26 % of their body weight within a week, an effect that was completely reversed by losartan (an angiotensin II receptor type 1 receptor antagonist) [67].

**Oxidative stress**

There is a wealth of evidence suggesting that oxidative stress is associated with chronic diseases and it is assumed that an increase in ROS directs muscle cells into a catabolic state that leads to muscle wasting [30, 70, 71]. In cachexia, ROS are regarded as crucial players for muscle protein catabolism via their stimulation of the UPS [30]. Reaction products are measured as indirect markers of oxidative stress [30]. In cachexia, malondialdehyde (MDA) is regarded as one such indirect marker [30].

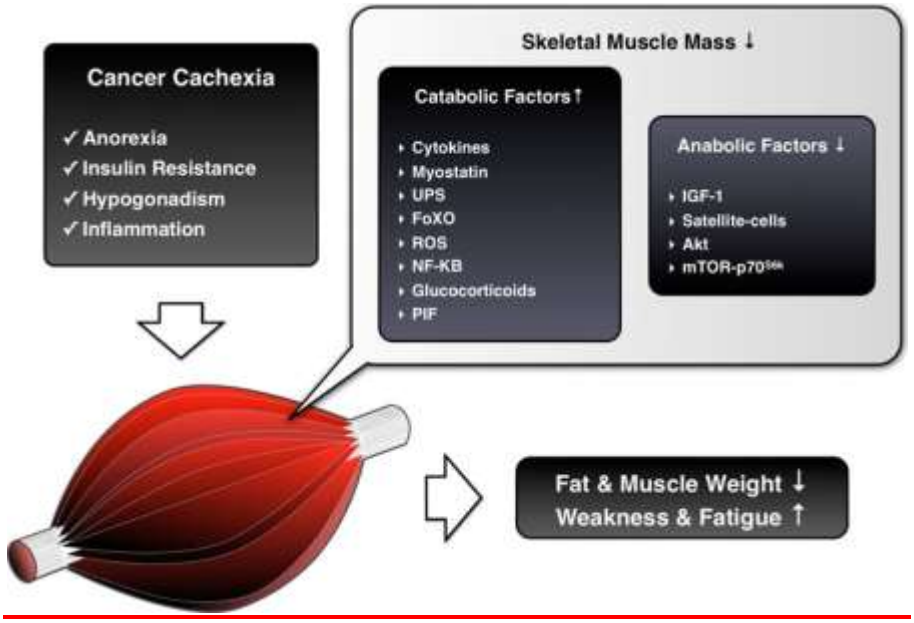



Fig. 2 An abbreviated diagram of skeletal muscle in cancer cachexia. In adults, muscle mass remains fairly constant in the absence of stimuli (e.g., exercise) and thus protein synthesis and degradation generally remain in balance. However, in cachectic situation, the balance of skeletal muscle has been shifted towards protein breakdown, finally leading to the weight loss, weakness, and fatigue that characterize cancer cachexia. In recent years, it has become evident that catabolic factors are up-regulated (e.g., cytokines, myostatin and members of the ubiquitin–proteasome system), whereas anabolic factors (e.g., insulin-like growth factor 1) are down-regulated in cachexia muscle wasting. IGF-1 Insulin-like growth factor 1, FoxO forkhead box O, UPS ubiquitin–proteasome system, ROS reactive oxygen species, NF-jBPIF tumor-released proteolysis-inducing factor, mTOR mammalian target of rapamycin, p70S6K p70 S6 kinase.

## Anabolic hormones

There is a relative deficiency or resistance to anabolic hormones in cachectic states. Up to 50 % of men with metastatic cancer present with low concentrations of testosterone prior to chemotherapy [74]. A reduction in testosterone might lead to reduced bone mass, muscle strength, and sexual function in both men and women [75, 76]. Low concentrations of testosterone and other anabolic hormones are major contributors to cachexia-related wasting of skeletal muscle [77]. However, with respect to a correlation between body composition (including muscle mass) and the concentration of anabolic hormones, conflicting results have been reported in the current literature [30, 74, 78, 79].

## C-reactive protein

A key (but often variable) component of cachexia is hypercatabolism that is directly caused by tumor metabolism, systemic inflammation, or other tumor-mediated effects. The most widely accepted index of systemic inflammation is serum CRP [83]. CRP plasma values are positively correlated with weight loss, the occurence of cachexia, and recurrence in advanced cancer [84]. Its role as a predictor of survival has been shown in multiple myeloma, melanoma, lymphoma,

ovarian, renal, pancreatic, and gastrointestinal tumors [84, 85]. Recent studies suggest that CRP is much more than a mere marker of the body's inflammatory load [86, 87].

Weight loss is a complaint of 15–40% of cancer patients and indicates poor prognosis. Cytokine induction in cancer has been well described. Peripheral and central mechanisms have been implicated (**Figure 3**, A and B). Cytokine production in malignant disease increases corticotrophin releasing factor, a potent anorectic agent, and, in concert with prostaglandins, suppresses the production of the orexigenic agent neuropeptide Y (80, 81). Proteolysis is stimulated within muscle by activation of the proteasome system and transcription factor NF-_B. Cytokines also delay gastric emptying, lower serum albumin concentrations, and enhance lipolysis (82, 83). Lipid mobilizing factor, a zinc _2-glycoprotein, activates cyclic adenosine-5-monophosphate in adipocytes, which results in the release of free fatty acids and glycerol into the circulation (84). Excessive lactate production from tumor cells exacerbates energy wasting by inducing the Cori Cycle in the liver and extrahepatic tissues (80).

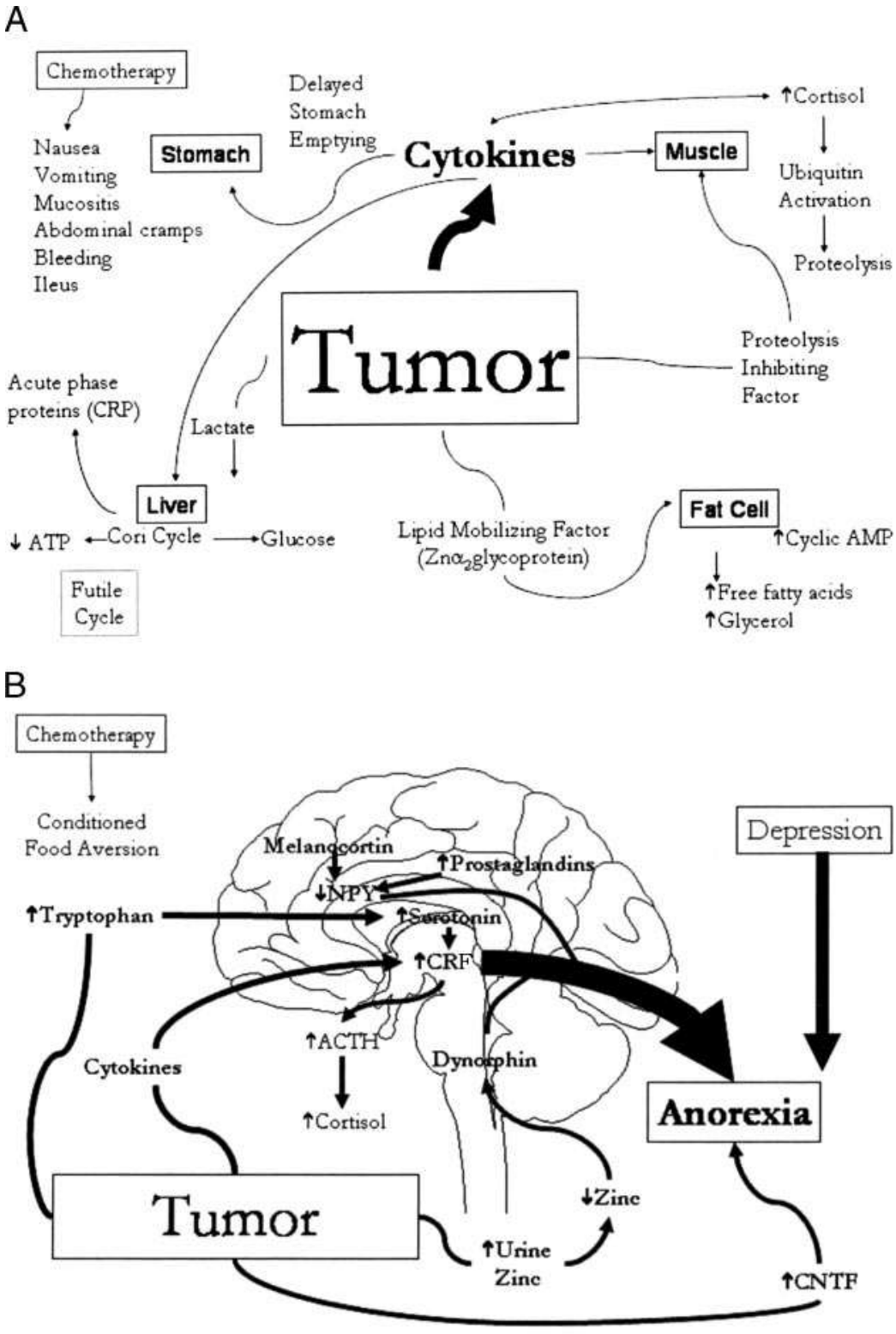



**FIGURE 3.** The peripheral (A) and central (B) mechanisms producing anorexia-cachexia syndrome in cancer. CRP, C-reactive protein; NPY, neuropeptide Y; CRF, chronic renal failure; ACTH, adrenocorticotrophic hormone; CNTF, ciliary neurotrophic factor.

## Protein Metabolism

Tumors have been known not only as "glucose eaters" but also as "nitrogen sinks", depleting the host of protein mass and resulting in characteristic alterations in protein metabolism. Several investigators have suggested that redistribution or translocation of peripheral proteins to support visceral or tumor protein synthesis is an essential feature of amino acid metabolism in cancer cachexia68. Because the rate of protein synthesis in human tumors is approximately the same as that of the tissue of origin69, and human tumors rarely exceed 1% of body mass70, the observed alterations in whole-body protein metabolism are unlikely to be secondary to the tumor itself, but rather to tumor-influenced alterations in host protein metabolism71.

### *Aminograms*

Basal postabsorptive aminograms in several homogeneous groups of patients with different malignancies have been reported with variable results. Only one paper by Clarke et al.72 showed elevations of alanine, isoleucine, and lysine, but all the others showed either decrease or no alterations. Heber et al.12 demonstrated decreased alanine levels in patients with advanced lung cancer. Those may support the hypothesis that gluconeogenesis from alanine and other gluconeogenic precursor proteins is increased. In 55 patients with a variety of tumors, proline levels were significantly reduced in lymphoma and sarcoma patients. Patients with esophageal cancer and weight loss demonstrated a marked reduction in all circulating amino acids except BCAA. No cancer-specific amino acid profile has emerged from the studies so far published73,74. However, it appears that patients with extraintestinal nonobstructive malignancies have minimal aberrations in their amino acid profiles, and it is possible that with more advanced malignancy with weight loss, more profound changes in amino acid concentrations occur.

### *Whole-body protein metabolism*

With few exceptions, whole-body protein turnover, synthesis, and catabolism have been reported to be elevated in both tumor-bearing animals75 and cancer patients. Those changes are not tumor-site specific but may be related to the advancement of the tumor. Shaw et al43 examined rates of whole-body protein synthesis and catabolism by isotopic infusion of alpha-[15N]-lysine and [15N]2-urea in 20 patients with advanced- weight-loss (AWL) upper gastrointestinal cancer, 7 patients with early non-weight-loss (ENWL) lower gastrointestinal cancer, and a group of volunteers. ENWL cancer patients and normal volunteers had similar protein dynamics, and in both groups, glucose infusion resulted in a significant decrease in protein loss. In AWL cancer patients, the rate of net protein catabolism was significantly higher than in either the volunteer or ENWL group ($p<0.05$). Glucose infusion did not result in a decrease in net protein catabolism. TPN significantly decreased net protein catabolism from 2.24+0.30 to 0.17+0.09 gm/kg/day ($p<0.01$). This decrease was due to the combined effect of a significant decrease in whole-body protein catabolism coupled with an increase in whole-body protein synthesis. Increase in whole-body protein catabolism—and whole-body protein synthesis to a lesser extent—in patients with cancer cachexia from a variety of tumors (n=47) was also confirmed in the subsequent study by the same group by intraoperative isotopic infusion of 14C-leucine83. They concluded that patients with cancer cachexia were actively losing protein as a result of an increase in whole-body protein catabolism that was only partially compensated for by an increase in whole-body protein synthesis. In a patient group studied by Borzotta et al.79, patients with advanced

malignancy or stage 4 cancer had significantly greater protein turnover, synthesis, and catabolism than patients with localized disease. Similarly, significant correlation between alterations in protein metabolism and stages of disease was documented by Carmichael et al.68.

***Skeletal muscle protein metabolism and regional amino acid kinetic study***

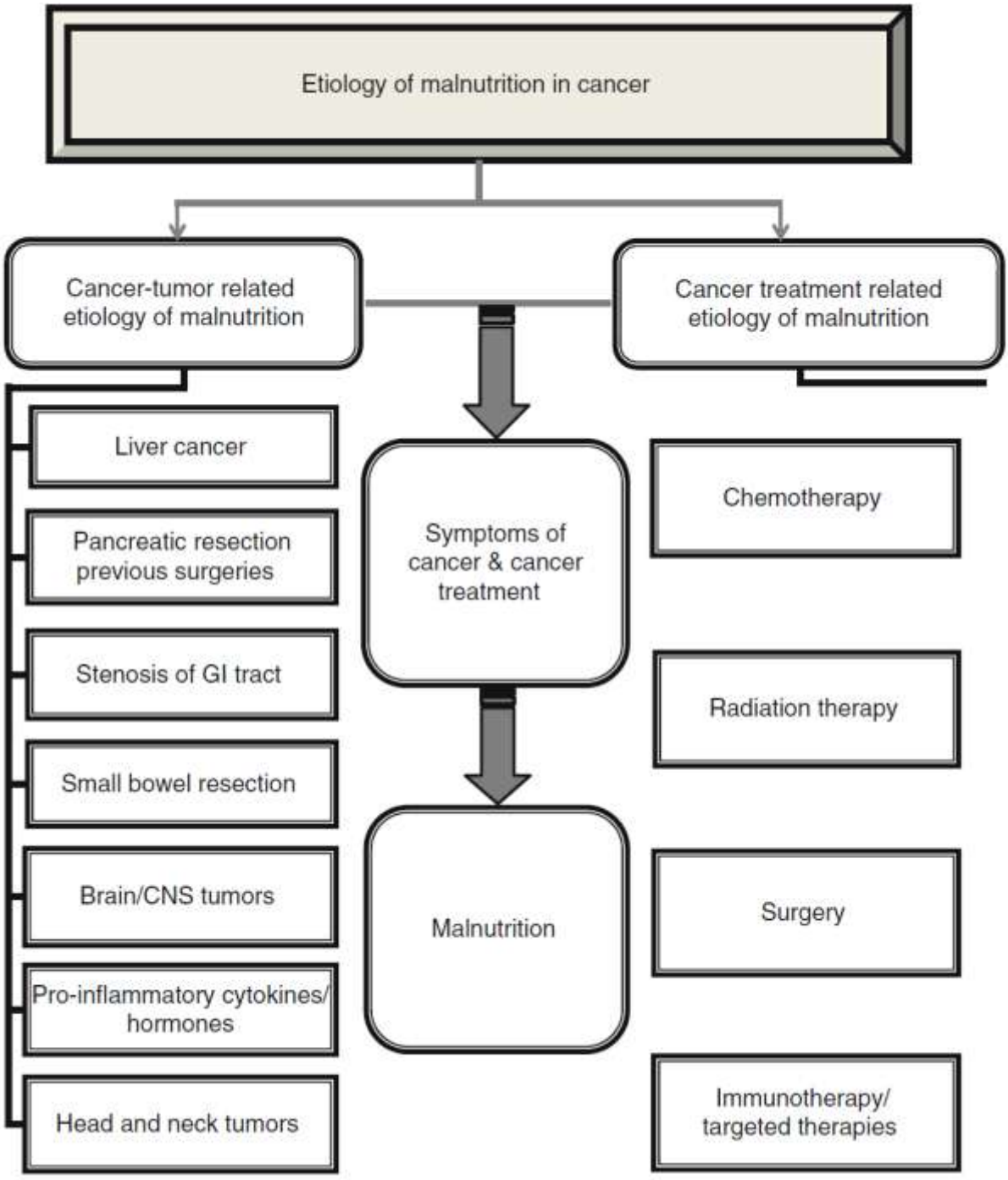
A common effect of tumor-bearing on protein metabolism in skeletal muscle has been shown to be depressed protein synthesis and increased protein breakdown. Clark et al.90, demonstrated those changes in the skeletal muscle in rats bearing the Wealker 256 carcinoma. Gastrocnemius muscle weight, RNA/DNA ratio, and incorporation of 14C-valine were significantly decreased. Incorporation of 3H-lysine into protein in the gastrocnemius polysome preparation was decreased, and net tyrosine release and 14CO2 production from 14Cleucine, representing protein degradation, were increased. Lundholm et al.85,77 examined the regional amino acid kinetics in rectus abdominus muscle obtained at surgery from 43 cancer patients with a variety of tumors and 55 controls. They demonstrated a significant decrease in the in vitro incorporation of 14C-leucine into skeletal muscle protein and an increase in the fractional degradation rate of proteins in cancer group compared with control. Emery et al.77 confirmed the significantly decreased protein synthesis in 5 cancer patients with weight loss by 13C-leucine enrichment in quadriceps protein obtained by percutaneous biopsy. Protein synthesis in muscle was 0.030%/hour in cancer patients and 0.198 in controls ($p<0.01$). Although most claimed decreased protein synthesis rates in the muscle, only one group found the fractional synthetic rate of protein in rectus abdominus muscle to be increased in cancer patients with cancer cachexia83. Contrary results were also reported. Newman et al.91, evaluated forearm phenylalanine exchange kinetics by infusion of L-phenylalanine under baseline and postabsorptive conditions in 16 cancer patients and 12 healthy controls and found no significant difference in phenylalanine kinetics in the basal state. Indirect evaluation of skeletal muscle protein catabolism by 3- methylhistidine documented no increase in cancer patients92. Whether those differences derive from differences in methodology or different types of tumor or stages is not clear.

***Hepatic protein metabolism***

Generally, protein synthesis in the liver has been reported to be increased in the tumor-bearing state. In the MCA 101 tumor-bearing mouse, increased incorporation of leucine in liver tissue was documented by Lundholm et al.93. They suggested that the tumor-bearing state was associated with an increased translational capacity.. Several systems have been defined as mechanisms of amino acid transport in liver. In the Fisher344 rat with MCA sarcoma, both System N (glutamine) and System y+ (arginine) were increased in the presence of the tumor, while System A (MeAIB) was unaltered. The observation that hepatic glutamine transport activity remained augmented after tumor resection longer than any other transport systems studied suggested a key role for this amino acid in overall hepatic nitrogen metabolism and might partially explain the persistent glutamine depletion that was characteristic of the tumor-bearing host94. The arginine pathway, which plays a pivotal role in regulating ureagenesis, polyamine biosynthesis, and nitric oxide production, was significantly stimulated in liver of the tumor-bearing Fisher 344 rats. This response was mediated by an increase in activity of System y+95. In human studies, an increased in vitro incorporation of 14C-leucine into homogenized hepatic proteins of cancer patients compared with normal controls was demonstrated85. Increased fractional synthesis rates (FSR) of protein in liver ($p<0.05$) and of albumin ($p<0.01$) have been confirmed in vivo in cancer cachexia patients compared with either non-weight losing

cancer patient or normal control83. Patients with NWLC had a mean FSR of protein in liver of 18.3%+2.2% per day. In contrast, the corresponding value in the patients with cancer cachexia was 29.7%+5.0% per day.

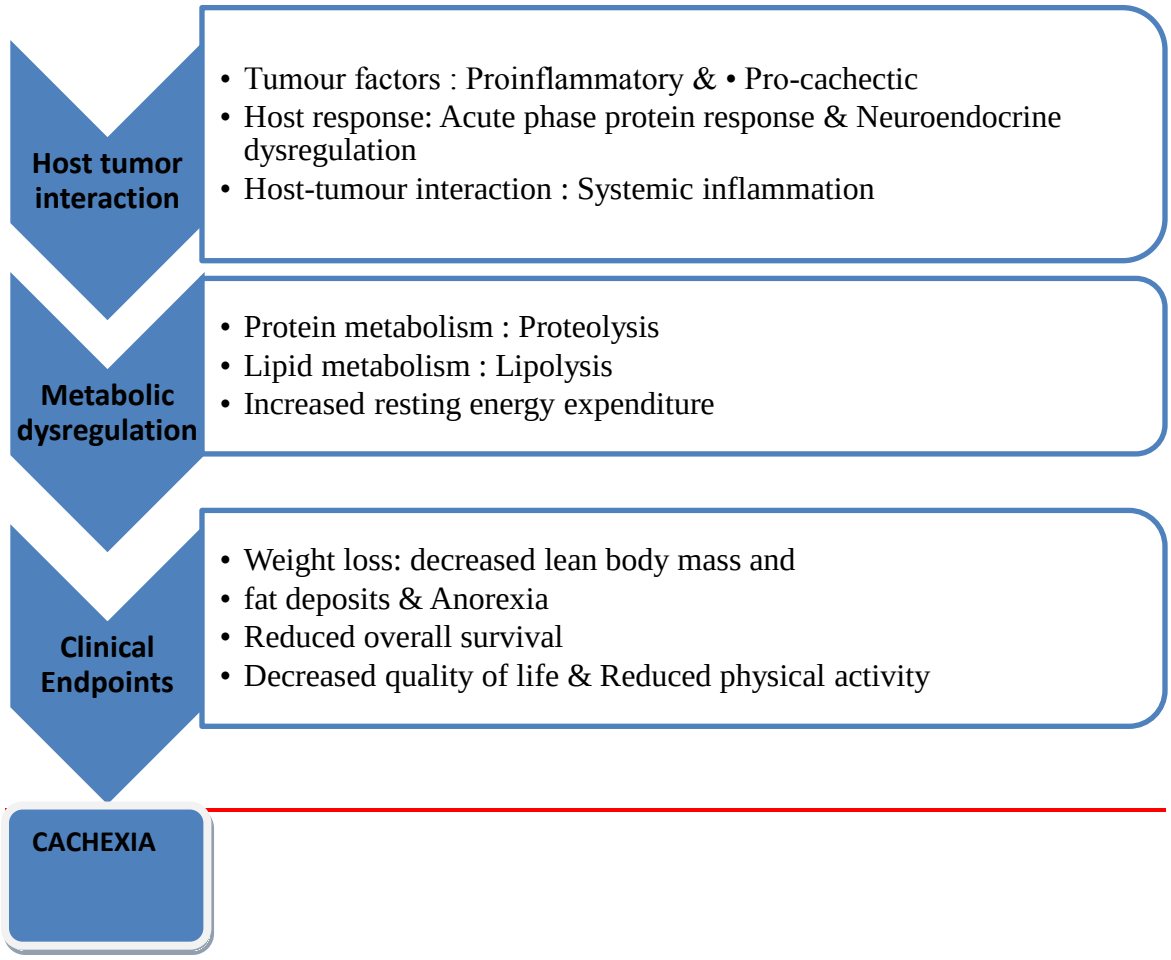
## ETIOLOGY OF CACHEXIA IN CANCER



*Causes of Cachexia*

| Causes of Cachexia | Patients Affected | Interventions |
|---|---|---|
| Cancer by-products | Cytokines; tumour necrosis factor, interleukin 1, leptin | Megestrol acetate, NSAIDS, adenosine triphosphate, corticosteroids |
| Depression or delirium | May cause or be caused by anorexia/cachexia | Haloperidol, anti-depressants, counseling, support |
| Dysphagia | Head, neck or esophageal tumours | Enteral feeding (gastrostomy preferred), stent, swallowing assessment, laser/ radiation, pain control with topical anesthetics or systemic analgesics |
| Gastrointestinal disturbances | Obstruction or constipation | Bowel regime, domperidone, metoclopramide or peripheral opioid antagonists and interventions for obstruction |
| Malabsorption syndrome | Fats and carbohydrates not metabolized/absorbed | Corticosteroids, megestrol acetate, omega 3 fatty acids |
| Treatment toxicities: mucositis, nausea/vomiting | Radiation, chemotherapy, medications | Treat according to toxicity |
| Uncontrolled symptoms: pain, dyspnea, constipation, and nausea/vomiting | Patients with advanced disease processes | Control symptoms to increase appetite and quality of life |
| Xerostomia, altered oral condition or taste | Infection, poor hygiene, dehydration, medication, taste bud alteration | Saliva substitutes, good oral hygiene and nutrition, zinc supplements |

## CLINICAL CONSEQUENCES OF CACHEXIA




## TREATMENT GOALS IN CACHEXIA, CURRENT STANDARD OF CARE

The European Palliative Care Research Collaboration (EPCRC) has developed evidence-based recommendations for the classification and treatment of cachexia in advanced cancer patients [97]. These treatment guidelines focus on patients with advanced cancer that are likely to suffer from refractory cachexia. Many of these patients are receiving palliative care, and life expectancy often is short. Only little cachexia-specific research has been done on this patient group, and the EPCRC treatment guidelines had to consider whether research results taken from other disease stages could be applicable for patients with advanced and incurable disease with refractory cachexia [97]. Management of cachexia must take into account the patient's prognosis [97], as it may take several weeks for patients to respond to anti-cachectic treatment [97]. For patients with a short life expectancy, treatment options for cachexi may add to the disease burden without offering adequate symptom relief and thus may not be appropriate [97]. Health care professionals should discuss all treatment options with the patient and ensure that they are well informed about available treatments and expected treatment outcomes [97]. All patients should have equal access to appropriate assessment and management of cachexia, whether they are receiving home care, day care, or are hospital inpatients [97]. The best way to treat cancer

cachexia is to cure the cancer, but unfortunately this remains an infrequent achievement among adults with advanced solid tumors [98, 99]. Therefore, the treatment goal for cachexia should be the reversal of the loss of body weight and muscle mass with a variety of pharmacological agents (Fig. 3) [99]. As a minimal goal, body weight should be maintained and further loss prevented [97]. The treatment approach should be multimodal and similar to treatment used in patients with pre-cachexia [97]. This includes detailed assessment and repeated monitoring, vigorous nutritional support, anti-inflammatory treatment, treatment of secondary gastrointestinal symptoms and other causes for decreased oral nutritional intake as well as evaluation of anti-neoplastic options to reduce the catabolic drive of the cancer [97]. However, for refractory cachexia, the primary treatment goal should not be reversal of weight loss, but the alleviation of cachexia-related symptoms and an overall increase of well-being [97].

***Goals of Therapy***. Clearly since cancer cachexia is associated with a poor prognosis, the aim of management is often to improve symptoms and quality of life. It is noted that a response to chemotherapeutic treatment by shrinkage of the tumour burden often leads to improvement in the cachectic state. The primary endpoints of optimal treatment of cancer cachexia are improvements in lean body mass, resting energy expenditure, fatigue, anorexia, quality of life, performance status, and a reduction in pro-inflammatory cytokines. A greater understanding of the process of inflammation and its fundamental role in the development of cachexia has led to new avenues opening up in the approach to management of the condition. The hypothesis is that effective treatment of cancer cachexia will improve performance status and quality of life and by inhibiting the process driving cachexia, survival may be improved. In patients who stop losing weight while receiving chemotherapy for gastrointestinal cancers, median survival is improved (15.7 months versus 8.1 months, $P = .0004$) [89].

## PHARMACOLOGICAL TREATMENTS

The clinical efficacy of medical therapy for CIC has been the subject of considerable research during the past several decades, beginning in the 1990's with an increase in AIDS –related wasting. Research originally focused on reversing starvation with the use of appetite stimulants such as megestrol acetate and tetrahydrocannabinol, which while effective had questionable impact on quality of life and no impact on survival. As AIDS and advanced cancer are catabolic states, studies have examined the role of specific growth factors as well as anabolic steroids, and these data are reviewed below. When the role of inflammation in cancer and the APR was discovered, attempts to attenuate neoplastic inflammation lead to work with non-steroidal anti-inflammatory drugs (NSAIDS) and TNF-α inhibitors. Research continues to progress with ghrelin and ghrelin agonists, and the identification of new targets such as the ubiquitin-proteasome pathway in hopes of maintaining lean body mass and preserving nutritional status in cancer patients.

*4.3. Pharmacological Agents.* Pharmacological options are summarised in Table 4. Among orexigenic agents, megestrol acetate is by far the most widely prescribed and at least 15 randomised controlled clinical trials have demonstrated that this drug, at doses ranging from 160–1600mg/d significantly improves appetite with respect to placebo [118]. A recent Cochrane meta-analysis reported that it improves weight gain and appetite in cancer patients [29].

Although this increase in appetite is very desirable for both patients and their carers, inmost of these trials no definitive improvement in global quality of life was observed [29]. Anti-inflammatory agents (COX inhibitors) can reduce weight loss and aid maintenance of performance status in advanced cancer [119]. The COX-2 inhibitor, meloxicam showed activity against PIF-induced proteolysis, prior to its withdrawal from the market [120]. Beta-adrenoreceptor blockade can reduce resting energy expenditure in patients with cancer ($n$ = 10) but have not been trialled in largerscale studies [121]. They are thought to inhibit proteolysis and lipolysis [122] and have been shown to downregulate catecholamine-induced catabolism in burns patients [123]. Agents which reduced cytokine levels such as thalidomide and pentoxifylline have only shown modest or minimal activity. At RCT, thalidomide has been shown to attenuate weight loss and lead to improved physical function [35]. Pentoxifylline did not have any clinical benefit. Specific antitumour necrosis factor- (TNF-)$\alpha$ agents, etanercept and infliximab, did not show any positive effect on appetite or body weight in RCTs [124, 125]. Corticosteroids, although widely used, have significant side effects including protein breakdown, insulin resistance, water retention, and adrenal suppression and tend to be used during the preterminal phase of patient illness [23, 126]. Anabolic steroid derivatives such as nandrolone and oxandrolone have not been studied in clinical trials in a cancer cohort. Insulin [27], ATP infusions [28], and melatonin [41] have produced modest positive effects in small clinical trials and require further substantiation.

| | Agent | Clinical effect (RCT)# | Hypothetical mechanism of action |
|---|---|---|---|
| **Anabolic agents** | Corticosteroids | Improves anorexia and weakness; no improvement in weight or calorie intake [23–25]; well tolerated; effects short lasting | Not established. May inhibit prostaglandin metabolism and central euphoric effect |
| | Nandrolone decanoate | Decrease in weight loss [26] | Not established. Promote protein nitrogen accumulation |
| | Oxandrolone | No published randomised clinical trials in cancer cohort | Not established |
| | Insulin | Increases whole body fat and carbohydrate intake [27] | Not established |
| | Adenosine Triphosphate (ATP) | Stabilises weight loss and increases energy intake[28] | Not established |
| **Appetite stimulants** | Progesterones: Megestrol acetate (MA) | Improves appetite, calorie intake | MA: may increase the central appetite |

| | | | |
|---|---|---|---|
| | Medroxyprogesterone (MP) | and weight (not lean body mass) [29] | stimulant neuropeptide YMP: reduces serotonin and cytokine production by PBMCs [30] |
| | Cannabinoids: Dronabinol | No benefit when added to MA; inferior to MA when used alone [31]. No increase in appetite or QoL [32] | May act on endorphin receptors, reduce prostaglandin synthesis or inhibit IL-1 secretion [33] |
| | Cyproheptadine | No improvement in weight gain | Serotonin antagonist with antihistaminic properties |
| **Cytokine inhibitors** | Thalidomide | Attenuates weight loss, increases lean body mass [35] | Immunomodulatory: downregulates TNF-$\alpha$ (by destabilising mRNA [36]), NF$\kappa$B, pro-inflammatory cytokines, COX2 [37] |
| | Pentoxifylline | No improvement in appetite or weight in cachectic patients [38] | Phosphodiesterase inhibitor: inhibits TNF gene transcription |
| | Eicosapentaenoic acid (EPA) | Cochrane meta-analysis: insufficient evidence to establish whether EPA is better than placebo [39] | In vitro attenuates increased cAMP activity and lipolysis by LMF [40] |
| | Melatonin | Improves cachexia (term not defined) and one year survival increased in advanced NCSC lung cancer [41] | Immunomodulatory [42], Downregulates TNF production [43] |
| **Anti-** | Non-steroid anti- | Reduced | Not established. May |

| | | | |
|---|---|---|---|
| **inflammatories** | inflammatory drugs | inflammatory markers, reduced resting energy expenditure, preservation of total body fat [44] | downregulate systemic inflammatory response to tumour |

**Appetite stimulants**

Reversing the effects of cancer cachexia does not appear to be influenced by stimulating the appetite [100]. Thus, the decision to use an orexigenic drug should be based on tolerance of the side effects, cost effectiveness, and treatment burden [100]. Current studies are investigating an approach of drug combinations to reverse cancer cachexia [101, 102]. A recent study with 332 patients comparing medroxyprogesterone, megestrol acetate, oral supplementation with eicosapentaenoic acid, L-carnitine, and thalidomide found that the combination therapy was superior to any of the other treatment arms with single drug treatment [102]. Combination therapy led to increased lean body mass, decreased resting energy expenditure, and improved appetite [102].

Until an effective intervention for reversing cancer cachexia is developed, early intervention with nutritional support and prevention of treatment-related morbidities (e.g., nausea, vomiting, diarrhea, dysphagia, pain, or depression) is advised [102, 103]. Progestational drugs, cannabinoids, and cyproheptadine are used in the clinic as appetite stimulatus in the therapy of the cancer-induced anorexia and cachexia syndrome [99]. These drugs have been shown to be partially effective in reversing or maintaining the symptom of body weight loss in patients with chronic illness [99]. Cannabinoids are highly liquid-soluble substances with delta-9-tetrahydrocannabinol (THC) as an active ingredient that wor k synergistically, additively, or even antagonistically when ingested together (e.g., by smoking marijuana). Appetite stimulation and body weight gain are well-recognized effects of using marijuana and its derivatives [99]. This may have significant implications for the clinical usefulness of marijuana or its individual compounds in treating cachexia.

Dronabinol is the synthetic oral form of THC, which is the active ingredient responsible for the appetite-stimulating effect [99, 104–106]. Dronabinol and marinol (in the United States) and nabilone (in Canada) have been used as antiemetics in cancer, with many studies demonstrating their efficiency in treating chemotherapy-induced nausea and vomiting [99]. Several studies of THC in advanced cancer-associated anorexia have shown some improvement in mood and appetite, with either no or some improvement in body weight [107, 108]. However, randomized, controlled trials are needed to better determine the efficacy and usefulness of THC in cancer cachexia. The effects of cannabinoids are mediated via specific receptors. Two types of cannabinoid receptors, CB1 and CB2 have been detected. However, the precise mechanism by which cannabinoids exert their effect has yet to be clarified. It has been shown that almost 20 percent of the cancer patients receiving chemotherapy along with dronabinol as an antiemetic experienced side effects, such as euphoria, dizziness, somnolence, and confusion resulting in a dose reduction or less frequently in withdrawal of the treatment [106]. It has been suggested that

the drug could be taken at bedtime to avoid some psychotomimetic effects and that it might produce long-lasting appetite stimulation for 24-h period following ingestion [104].

Cyproheptadine is an antiserotoninergic drug with antihistaminic properties that has been shown to have a slight appetite-stimulant effect in a number of human conditions [109]. A randomized, controlled trial found mild appetite stimulation in patients with advanced cancer, although it did not prevent progressive weight loss [110]. Considerable evidence, both in humans and experimental animals, suggests that anorexia may be mediated by increased serotonergic activity in the brain. Its blockade, therefore, might be beneficial in reducing symptoms [111, 112]. Cyproheptadine also appeared to stimulate appetite and decrease diarrhea in patients with advanced carcinoid tumors [113]. Studies on the effects of cyproheptadine in progressive weight loss in patients with cancer or other causes of cachexia suggest that cyproheptadine has a beneficial effect on appetite stimulation but only slight effects on weight gain [110, 114, 115]. 5-hytroxytryptamine type 3 (5HT3) receptor antagonists, such as ondansetron and granisetron, have entered widespread clinical use as antiemetics for cancer chemotherapy [99].

**Other orexigenic agents**

The orexigenic mediator ghrelin has been reported as having a key role in increasing appetite and, therefore, food intake. Ghrelin is an endogenous ligand for the growth hormone secretagogue receptors [137, 138]. It is synthesized principally in the stomach and is released in response to fasting [138]. Ghrelin strongly stimulates GH secretion in humans [139–142] and does so more potently than GHRH by several fold under similar circumstances [143]. Furthermore, ghrelin and GHRH synergistically increases GH release [141]. GH regulates IGF-1 levels and increases muscle strength [144, 145], whereas GH enhances lipolysis, IGF-1 stimulates protein synthesis, myoblast differentiation, and muscle growth [143]. Evidence that ghrelin exerts anti-inflammatory actions has been accumulating [143]. Ghrelin induces the anti-inflammatory cytokine IL-10 [146, 147], suppressing the production of proinflammatory cytokines, including IL-1b, IL-6, and TNF-a both in vitro [148, 149], and in vivo [146, 150, 151]. Additionally, ghrelin inhibits the activation of NF-jB, which controls the production of multiple proinflammatory cytokines during inflammatory insults [147, 149, 150]. Although the molecular mechanisms and cellular targets mediating ghrelin inhibition of NF-jB activation remain to be determined, the vagus nerve may play an important role in the ghrelin-mediated inhibition of proinflammatory cytokine release [150, 152].

Nutritional support enhances quality of life but does not improve mortality rates associated with most cancers (85, 86). Excessive proteolysis in cancer-anorexia syndrome can be abated with anabolic hormones, _2 adrenergic agents, or cytokine inhibitors (87). Appetite stimulants such as dronabinol, an endogenous cannabinoid receptor agonist, and megesterol acetate (a cytokine antagonist) may be helpful. Data indicate that megesterol acetate is more effective than is dronabinol (88). Conflicting evidence exists regarding the efficacy of androgenic steroids.

Eicosopentaenoic acid decreases proinflammatory cytokines (89) and suppresses ubiquitin-proteasome-induced muscle proteolysis (90). Eicosopentaenoic acid stabilized weight in some trials of patients with advanced cancer (91). Recent studies have also shown significant increases

in weight gain, lean body mass, and quality of life after treatment of cachexia with eicosopentaenoic acid (92). A pilot study that examined the effect of infliximab, an immunoglobulin G antibody that blocks TNF-_ receptors, showed weight stability in 1 of 4 patients with metastatic small cell lung cancer (93). Cori Cycle inhibitors, such as hydrazine, are not helpful (80).

***4.2. Eicosapentaenoic Acid.*** Eicosapentaenoic acid (EPA), a long-chain polyunsaturated fatty acid (PUFA) of the omega- 3 (n-3) family, has been studies in relation to cancer cachexia for over 15 years. It is of interest in the context of cancer cachexia as it has potential to impact on both the underlying metabolic abnormalities of tumour-induced weight loss, as well as modulation of immune function. When EPA is consumed at levels above that normally found in the diet, it replaces arachidonic acid (AA), an n-6 PUFA, in cell membrane phospholipids. It then acts as a substrate for the production of the 3 series prostaglandins and the 5 series leukotrienes. Eicosanoids synthesized from the n-3 PUFAs (i.e., EPA) rather than the n-6 PUFAs (i.e., AA) have lower potential for promoting inflammation. Modulation of dietary fatty acids can therefore have an impact on many immune processes such as proliferation, phagocytosis, cytotoxicity, and cytokine production [111]. Despite initial studies showing anabolic effects, principally gains of lean bodymass, improvements in grip strength, quality of life, and reductions in IL-6 and PIF could be achieved in a variety of cancers [99], including pancreatic cancer [112, 113], lung cancer [114], and colorectal cancer [115], analysis of RCTs only, using the Cochrane approach, did not show any differences between EPA supplementation and placebo [39]. Whether this is a true representation or a reflection of the advanced cachexia of participants or inherent differences in EPA metabolism between individuals (with only a proportion of patients able to respond to EPA) needs further examination. On subgroup analysis, patients who comply with EPA supplementation seem to have improved lean body mass [116].

EPA-enriched oral nutritional supplements (ONSs) have been compared to megestrol acetate in the North Central Cancer Treatment Group trial of 421 patients with weight loss, poor intake, and anorexia [117]. In a 3-month intervention period, patients were randomized to either EPAenriched ONS plus placebo liquid suspension, standard ONS plus megestrol acetate suspension, or EPA-enriched ONS plus megestrol acetate suspension. Weight gain was highest in the megestrol acetate group but unfortunately body composition was not assessed and so changes in water weight cannot be controlled for. There was no difference in survival, appetite, or quality of life scores between the groups, however patients on megestrol acetate reported higher rates of impotence. The fact that an EPA enriched ONS scored as well as drug therapy on certain clinical endpoints (e.g., survival and global quality of life) underscores the limitations of each treatment.

**Megestrol Acetate**

Megace®, or megestrol acetate (MA), is a synthetic derivative of progesterone, and the most widely used drug used to treat CIC.lv The precise mechanism of action of MA is unknown but research in murine models suggests that its effect may be partially mediated by neuropeptide Y, a potent centrally acting appetite stimulant.lvi A number of human studies show that various doses of MA stimulate appetite and increase weight gain; however more detailed body

composition studies suggest that the weight gain is largely an increase in fat mass, while performance status and QOL are generally not affected.lvii, lviii. A 2005 Cochrane Database Review of 30 trials with over 4000 patients evaluated the efficacy, effectiveness, and safety of megestrol acetate in CIC. The review showed a benefit of megestrol acetate with regard to appetite improvement and weight gain in cancer patients, but no statistically significant conclusion about QOL changes could be drawn due to heterogeneity.31 There was insufficient information to define the optimal dose of megestrol acetate although therapeutic doses typically ranged from 100mg to 1600mg per day, with efficacy shown between 400-800mg daily.lix A 2008 review by Lésniak et al. noted that the cancer patient study population experiences high mortality and progressive weight loss regardless of treatment. There was no difference between MA and placebo on survival. MA increases appetite (number needed to treat (NNT): 3) and leads to weight gain (NNT: 8).lx The side effects of megestrol acetate include an increased risk of thromboembolism at doses exceeding 800mg per day, hypogonadism, transient adrenal insufficiency, and edema.lxi,lxii Given that MA increases fat mass and edema with no improvement in quality of life or survival, use of this agent has started to be abandoned in favor of catabolic therapies aimed at increasing or maintaining muscle mass.

## Tetrahydrocannabinol (THC)

Tetrahydrocannabinol (THC) is the main psychoactive substance found in the Cannabis sativa plant. Synthetic THC is known as dronabinol and is available as a prescription medication as Marinol® which is prescribed for intractable cancer pain. The starting dose is 2.5 mg orally twice daily with titration up to 20 mg per day. THC has been found to influence the endocannibinoid system, a group of neuromodulatory lipids and their receptors, that are involved in pain perception, emesis and reward pathways.lxiii,lxiv Studies have shown that THC can stimulate appetite and promote food intake in healthy volunteers lxv,lxvi and patients with AIDS.lxvii A number of studies have been conducted to evaluate the effects of THC in patients with CIC. A phase III study involving 243 patients with advanced cancer experiencing cancer-related anorexia-cachexia were randomly assigned (2:2:1) to receive cannabis extract (standardized for 2.5 mg THC and 1 mg cannabidiol) or THC (2.5 mg) or placebo orally, twice daily for 6 weeks. Appetite, mood, and quality of life (QOL) were monitored and cannabinoid-related toxicity was assessed. An independent review board recommended that the trial be closed after interim analysis of 156 patients due to insufficient differences in the primary end point: change in appetite from week 0 to week 6 assessed with the visual analog scale. Subsequent intent-to-treat analysis showed no statistically significant differences between the three arms for appetite, cannabinoid-related toxicity or QOL.lxviii

## Growth Hormone and Anabolic Steroids

With the understanding that MA increased fat mass with no improvement in performance status or survival, research focused on maintaining the cachectic patient's lean body mass in efforts to improve performance status and quality of life. Anabolic factors such as growth hormone (GH) and steroid hormones were investigated. GH has been shown consistently to stimulate muscle protein synthesis in catabolic states and historically was prescribed to AIDS

and chronic obstructive pulmonary disease (COPD) patients suffering from cachexia.lxx,lxxi Prior animal studies had shown that the GH–IGF-1 system plays a role in the development and progression of cancer and there has been hesitation among oncologists to use GH for treatment of CIC owing to concern that GH may stimulate tumor growth.lxxii It is important to note that this hypothesis has not been proven in either animal or human studies. The rationale behind this theory is based on historical data when a hypophysectomy (along with oopehorectomy and adrenaletomy) were part of a complete endocrine ablative therapy for breast cancer. The hypothesis also develops from epidemiologic data showing that healthy persons with increased height (> 175cm) and rapid growth during adolescence were at higher risk for breast, prostate and colon cancer.lxxiii, lxxiv

Testosterone and its derivatives are steroid hormones that exert their effect through binding to cytosolic receptors, leading to an increase in protein synthesis and muscle mass.lxxv Testosterone also inhibits the macrophage mediated release of pro- inflammatory cytokines like TNF α, IL- 1β and IL-6 lxxvi,lxxvii and stimulates the release of IL-10, an anti-inflammatory cytokine.lxxviii Studies have shown positive effects of these anabolic agents on body weight, lean body mass and functional parameters in cachectic patients. However, most studies have been largely limited to patients with COPD and HIV-AIDS.lxxix,lxxx In these trials testosterone was prescribed as either testosterone cipionate or testosterone enanthate and administered intramuscularly or dermally to treat hypogonadal men. No trials have been conducted to date investigating the use of testosterone in patients with CIC. The side effects of testosterone limit its use.

## NSAIDS

NSAIDs have been shown to reduce the APR as well as resting energy expenditure and preserve body fat in patients with advanced cancer. Lundholm et al. evaluated the effect of anti-inflammatory treatment on tumor progression in 135 patients with solid tumors. Patients were randomized to receive placebo, prednisolone (10 mg twice daily), or indomethacin (50 mg twice daily) until death. Indomethacin prolonged mean survival compared to placebotreated patients. Survival analysis on all patients treated with either indomethacin or prednisolone demonstrated a significantly prolonged survival by anti-inflammatory treatment compared to placebo. Indomethicin prolonged survival when compared to the placebo group from 250 +/- 28 days to 510 +/- 28 days.lxxxix Lai et al. conducted a phase II clinical pilot trial investigating the effect of a 21-day course of Celebrex® (celecoxib) on body composition, inflammation, and quality of life (QOL) in 11 patients with cancer cachexia. Body composition, resting energy expenditure, QOL, physical function, and inflammatory markers were measured on days 1 and 21. Patients receiving the celecoxib had significant increases in weight and body mass index (BMI), and increases in QOL scores. The investigators noted that compliance was good with no adverse events.xc Mantovi et al. also initiated a prospective phase II clinical trial to test the effectiveness of celecoxib (300mg/day) for four months in 24 patients with advanced cancer. Endpoints included lean body mass, resting energy expenditure, and serum cytokine levels. There was a significant increase of lean body mass and decrease of TNF-alpha levels. In addition, the patients showed an improvement in grip strength, quality of life, and performance status. No grade 3 or 4 toxicities were reported.xci COX-2 inhibition is currently one of the more promising areas of CIC research

as this medical therapy directly targets the inflammatory APR of CIC and has shown to be well-tolerated with minimal side-effects.

**TNF-alpha Inhibitors: Infliximab, Etanercept, Adalimumab**

Anti-TNF-alpha therapies are currently employed for inflammatory conditions such as rheumatoid and psoriatic arthritis and Crohn's disease. As TNF-alpha has become increasingly implicated in the pathogenesis of CIC, thus, interest in evaluating these drugs as a possible therapy has evolved. Saraceno et al. used a population of patients under treatment for psoriatic arthritis to evaluate the effect of anti-TNF-alpha therapy on body mass index (BMI). The investigators examined the effect of either infliximab, etanercept, or adalimumab (experimental group) against a control group of patients on efalizumab or methotrexate which both are traditionally used for psoriatic arthritis treatment. The patients were treated for 48 weeks. At week 24 a significant increase in body weight and BMI in the anti-TNF-alpha treatment group compared to the control was observed.xcii

In another trial using rheumatoid arthritis patients, etanercept was evaluated for its effect on body composition. Twenty-six patients were randomly assigned to 24 weeks of treatment with etanercept or methotrexate (considered first-line therapy for rheumatoid arthritis). Body composition, physical function, disease activity, systemic inflammation, and the circulating insulin-like growth factor (IGF) system were measured at baseline (week 0) and at follow-up (weeks 12 and 24). Overall, no important changes in body composition were observed. Secondary analysis of six patients who gained weight during follow-up showed that patients receiving etanercept had an increase in fat-free mass. The investigators concluded that etanercept was not superior to methotrexate for the treatment of rheumatoid cachexia. But did note that TNF blockade seems to normalize the anabolic response to overfeeding and could be useful in treating anorexia and weight loss.xciii

More recently, Jatoi et al. conducted a double-blind trial randomly assigned 61 patients to infliximab/docetaxel versus placebo/docetaxel. The primary endpoint was greater or equal to 10% weight gain. No patient gained or exceeded an increase of 10% baseline weight, and the lack of efficacy prompted early trial closure. Appetite improvement was negligible in both arms. However, infliximab/docetaxel-treated patients developed greater fatigue and worse global quality of life scores. Tumor response rate and overall survival, were not statistically different between groups. Genotyping for the TNF alpha -238 and -308 polymorphisms revealed no clinical significance of these genotypes, as relevant to the loss of weight or appetite.xcv

**Ghrelin and ghrelin agonists**

Ghrelin is a peptide hormone secreted by the stomach and pancreas in response to fasting. Ghrelin binds to the growth hormone receptor in the hypothalamus to stimulate the release of growth hormone from the anterior pituitary. Ghrelin also increases hypothalamic expression of the orexigenic neuropeptides such as neuropeptide Y.xcvi Studies have shown that cachectic cancer patients can have higher levels of ghrelin compared to cancer and noncancer controls,

why these levels remain insufficient to significantly increase appetite to arrest weight loss is unknown.xcvii Higher ghrelin levels have also been correlated with cancer severity stages.xcviii Stasser et al. first attempted ghrelin administration to cachectic cancer patients. 21 patient were randomized to receive either 2 μg/kg or 8 μg/kg of human ghrelin as a 60-min infusion on two study days, seven days apart. A third study group was randomized to receive placebo on two study days, seven days apart. Ad libitum food intake tended to improve during ghrelin administration but this was not statistically significant. Nutritional intake did not differ between patients receiving ghrelin or placebo. No grade 3 or 4 toxicity or stimulation of tumor growth was observed. The peak increase of growth hormone, a biological marker of ghrelin action, was 25 ng/ml with lower-dose and 42 ng/ml with higher-dose ghrelin.xcix

Limited data is available on the effects of ghrelin receptor agonists. A phase I pilot study conducted by Garcia et al. examined an orally available ghrelin mimetic (RC-1291) at various doses daily and twice daily in healthy volunteers.ci Results showed that the agonist produced a dose-related increase in body weight without dose-limiting adverse effects. These authors also conducted a pilot double-blind trial in cachectic cancer patients and administered oral RC-1291 (50 mg/day) over a twelve-week period. Results showed a significant 1.3% increase in lean body mass compared to placebo that RC-1291 was well tolerated.cii

## NUTRITIONAL INTERVENTION:

The strong impact that cancer cachexia has on cancer patients' outcome and quality of life suggests that nutritional issues should be taken into consideration from the beginning of the natural history of cancer, a concept termed the parallel pathway [103]. Indeed studies of nutritional intervention that have reported a better weight maintenance in patients are in those who are treated in the "precachexia" phase, that is, prior to loss of >10% of body weight and prior to elevations of CRP. Dietary counselling with or without oral nutritional supplements has proven efficacy in stabilizing nutritional status in pre-cachectic patients [104, 105]. A nutritional assessment to seek reversible causes of weight loss is the first step in management in cachectic patients. Approximately 40% of cancer patients eat less than the 34 kcal/kg/day required to maintain weight [106]. The European Society of Parenteral and Enteral Nutrition (ESPEN) report in a consensus statement that there is Grade A evidence for intensive dietary counselling with food plus or minus oral nutritional supplements in preventing therapyassociated weight loss, preventing treatment interruptions and increasing dietary intake in gastrointestinal or head and neck cancer patients undergoing radio- or chemotherapy For patients with advanced cachexia (>10% weight loss, systemic inflammation and poor appetite) studies seeking to assess the effect of targeted nutritional advice and supplements have generally reported no significant improvement in nutritional status. Standard enteral or parenteral supplements do not appear to result in lean mass weight gain for the typical cancer patient [5, 98, 108]. The largest evaluation of the literature regarding nutritional supplementation (NS) (oral or tube) in cancer patients was the systematic review by Elia et al. (2006) showing no difference in mortality in patients undergoing chemotherapy/radiotherapy (4 RCTs) or surgery (4 RCTs) [109]. A systematic

review of parenteral nutrition in cancer patients showed no difference in mortality (19 RCTs), increase in total complication rates in those given parenteral nutrition (8 RCTs), and significantly lower tumour response rate in patients receiving parenteral nutrition (15 RCTs) [110]. This is likely because the inflammatory response of cachexia prevents anabolism. In many cases an attempt is being made to reverse or halt a rapidly advancing catabolic process and it is unrealistic to expect a reversal with calories and protein alone. The poor results observed with conventional nutrition support in cachectic patients led to the emergence of socalled nutraceuticals or immunonutrition supplements, in an attempt to nutritionally modify the metabolic milieu by providing anti-inflammatory substances, such as eicosapentaenoic acid (EPA), at levels much higher than that typically found in the diet.

In addition to nutrition support modalities, practicing oncologists may prescribe medical therapies designed to increase body weight and lean body mass, including megestrol acetate, tetrahydrocannibinol, oxandrolone, and non-steroidal anti-inflammatory drugs. A variety of experimental therapies are also being investigated for cancer-induced cachexia including tumor necrosis factor-alpha inhibitors and ghrelin infusions. We review the available data to support nutrition-oriented interventions in cancer-induced cachexia, including omega-3 fatty acids, aminoacid loading/protein supplementation, parenteral and enteral nutrition support, and food-derived compounds such as curcumin, reservatrol, and pomegranate.

Any nutrition intervention must first involve assessment of the patient's current dietary habits, either with informal conversation or with the 3-day food journal mentioned previously. Data regarding the success of dietary counseling in cancer patients experiencing CIC has been conflicting in the past, though has recently become a more common intervention in medical and radiation oncology practices. French oncology guidelines require systematic screening for malnutrition since 2007 and recommendations include oral supplementation as well as “immune-enhancing diets”.cxiii Hopkinson et al. discuss the need for nutritional assessment to identify erroneous dietary beliefs held by the patient and caregiver. The authors emphasize that: • a “healthy diet” as currently defined in our culture (i.e. low fat, high fiber, five portions of fruit and vegetables daily) has no proven benefit for someone with advanced cancer • patients will typically eat more of the things they enjoy or find easiest to eat • cold foods, soft foods and fluids can provide the same nutrients as cooked meals • cancer causes metabolic change that suppresses appetite, these changes are out of the patient's control and should not serve as an indication of not trying to eat, emotional weakness or giving up • and disagreements over food are common between patients and caregivers. Cxiv At this time, there is no agreed upon successful nutritional intervention for cancer-induced cachexia. Promising in-vitro and in-vivo data will be subsequently outlined, however need to be considered as part of a multi-modality approach.

A number of approaches have been taken to improve nutritional status in cancer patients. Attempts to raise energy and protein intake by counselling have been successful, but despite improvements over a three month period, no improvement in weight, anthropometric measures, response rate, survival, or quality of life have been demonstrated. 5 6 Disappointing results were also obtained when nutrient intake was increased by the parenteral route. The deleterious effects of parenteral nutrition (for example, increased infective complications) led the American College

of Physicians, in a position paper, to conclude ‘‘parenteral nutritional support was associated with net harm, and no conditions could be defined in which such treatment appeared to be of benefit’’. While the precise mechanism(s) of cachexia is unclear it is self evident that the inflammatory process is exceedingly strong in weight losing cancer patients. Thus the patient’s nutrient intake is dissipated by the hypermetabolism induced by the inflammatory state. Thus nutritional therapy, to improve survival in cancer patients, must make the inflammatory process its prime target.7 Among nutrients that may be effective in this respect are n-3 or omega-3, polyunsaturated fatty acids (n-3PUFA) and antioxidants.

The former have been shown to be particularly effective anti-inflammatory agents in rheumatoid arthritis.8 Moreover, the effectiveness of n-3 PUFA in modulating the inflammatory process has been demonstrated in a diverse range of clinical situations ranging from surgery9 to adult respiratory distress syndrome.10 Fearon’s group have pioneered the use of fish oil in the treatment of pancreatic cancer. The results of a number of small trials have been reported in which the oil, or the main n-3 PUFA that it contains (eicosapentaenoic acid (EPA)), has been demonstrated to reduce the high rates of weight loss in such patients.11

## Omega-3 Fatty Acids

The omega-3 fatty acids eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are found in fish oil and are known for their ability to reduce inflammation in the human body.

Omega-3 fatty acids as a nutritional intervention for cancer remains an area of intense interest particularly as it relates to the potential to improve response to cytotoxic treatments and reduce associated side effects, particularly muscle wasting. EPA and DHA are well recognized for anti-inflammatory propertiescxv,cxvi and these actions, together with EPA's ability to block ubiquitin-proteosome induced muscle proteolysis, probably account for EPA's favorable effect on wasting syndromes. Omega-3 fatty acids are found in thephospholipid (PL) membrane of cells. Fatty acid composition of plasma PL and different cell types (erythrocytes, neutrophils) reflect short and long term patterns of dietary fatty acid consumption, and are frequently used as indices of fatty acid status.cxvii Studies have shown that patients with advanced cancer have low amounts (<30% of normal values) of fatty acids in their plasma phospholipids.cxviii The potential impact of an essential fatty acid deficit is exemplified by data showing that survival is reduced by about half (approximately 8 months shorter) in cancer patients who have EPA below the range observed in an age matched healthy control group.cxix There is evidence to suggest improvement in muscle health when essential fatty acid supply is maintained. As discussed, sarcopenia is highly prevalent in the cancer population and affects patients in all body mass index (BMI) ranges (from underweight to overweight to obese). Sarcopenic individuals exhibit low concentrations of EPA and DHA in plasma.111 Given that n-3 fatty acids are deficient in cancer patients experiencing weight and muscle loss, supplementing n-3 fatty acids may provide a benefit. A.S.P.E.N. also encourages supplementation with n-3 fatty acids of 2g daily to help stabilize weight.

**Micronutrients**

As noted above, current data regarding nutrition support for CIC is conflicting, however targeted nutritional intake with dietary components is a consideration. Multiple epidemiological and animal model studies show that consumption of fruit and vegetables decreases the occurrence of variety of cancers.cxlvi,cxlvii,cxlviii,cxlix,cl As previously mentioned however, the benefit of fruit and vegetable consumption, as well as various micronutrients, appears to be the result of lifelong dietary habits as opposed to increase in consumption during a short period of time. The specific anti-cancer effects of the micronutrients in fruits and vegetables continue to be research targets and are popular with the general media and public. While the best treatment for CIC remains treatment of the underlying cancer, a review of nutritional therapies does warrant a word on micronutrients. Use of micronutrients and ensuring good nutritional intake in CIC is also attractive when considering the cost of other interventions. D ietary consumption of foods and herbal medicines is a convenient method of administering phytochemicals in a cost effective manner with minimal side-effects. Cli

**Vitamins and Minerals**

The need for vitamins and minerals is increased in this patient population. Oxidative stress and infl ammation contribute to several organ toxicities, including neurotoxicities, af ter common cancer chemotherapy regimens. Doxorubicin and other platinumbased therapies have been documented to cause the generation of free radicals and the induction of oxidative stress, associated with cellular injury [ 104 ]. The debate continues as to the safety of antioxidant use during chemotherapy to reduce oxidative stress, other than a multivitamin-mineral supplement that meets the current USRD A. Increased doses higher than the USRDA may not be recommended based on the safety and nutrient-cytotoxic agent interaction concerns, if administered during active therapy. In September 2005, studies were published [105, 106 ] warning against the concurrent use of antioxidants with cytotoxic therapies. Supplementing with antioxidants and anti-infl ammatory agents posttreatment may serve to “rescue” tissues from the effects of the oxidative damage, in addition to replenishing depleted status of these critical nutrients and reversing oxidative damage. However, these theories have not been tested in well-powered trials, in clinical trials targeting cancer patients.

**Fats/Lipids**

There are no recommended dietary allowances for lipids and carbohydrates in cancer patient populations.

**Curcumin**

Investigations into curcumin for CIC have been conflicting in mice. Researchers induced progressive muscle wasting in mice by implanting the MAC16 colon tumor and subsequent findings indicated that low doses of curcumin c3 (100 mg/kg body weight) was able to prevent weight loss and higher doses of curcumin c3 (250 mg/kg body weight) resulted in approximately 25 % weight gain when compared with the placebo-treated animals.clii A 2001 study was negative, with systemic administration of curcumin [1,7-bis(4-hydroxy-3- methoxyphenil)1,6-heptadiene-3,5-dione] (20 microg/kg body weight) for 6 consecutive days to rats bearing the highly cachectic Yoshida AH-130 ascites hepatoma. The curcumin inhibited tumor growth (31%

of total cell number) but showed no improvement on muscle bulk. Both the weight and protein content of the gastrocnemius muscle e in these mice significantly decreased as a result of tumor growth and curcumin was unable to reverse this tendency. The authors concluded that curcumin has little potential as an anticachectic drug in the Yoshida AH-130 ascites hepatoma tumor model.cliii

**Resveratrol**

Resveratrol (trans-3, 4′, 5-trihydroxystilbene) is a naturally occurring polyphenol found in the skin of red grapes and other fruits. Resveratrol has been explored by cardiovascular researchers due to its anti-inflammatory properties and ability to inhibit platelet aggregation. Resveratrol has also shown have anti-cancer effects in-vitro and data regarding CIC is conflicting. The most notable cancer research has shown that dermal application of resveratrol on mice, after UVB exposure, inhibited skin damage and decreased skin hyperplasia. cliv Additional in-vivo data on reservatrol supports anti-tumor affects in breast, prostate, esophageal and colon cancer.clv Resveratrol also inhibits various tumor promotion proteins, including cyclooxygenase (COX) -2. clvi Its anti-inflammatory properties make it an attractive therapy for CIC. Recently, Olivan et al. examined the anti-muscle wasting effects of multiple nutraceuticals such as genistein, resveratrol, epigallocatechin gallate and diallyl sulphide (DAS) in muscle cell cultures submitted to hyperthermia. All the nutraceuticals tested inhibited muscle proteolysis, including reservatrol.clvii

**Pomegranate**

The pomegranate (Punica granatum L.) is a fruit grown throughout the Mediterranean, Southeast Asia, and in the United States where it is found predominantly in California and Arizona. Pomegranate has been explored by multiple medical specialties including cardiology, infectious disease, and urology for a variety of conditions. Data has shown that there are multiple constituents of the pomegranate of medical interest and it appears that their synergetic affect is superior to that of a single agent. The promegranate's actions are as an antioxidant, anticarcinogenic, and anti-inflammatory. Cold pressed pomegranate seed oil has been shown to inhibit both cyclooxygenase and lipoxygenase enzymes in vitro.clxi As previously discussed, COX-2 expression is increased in cachexia due to TNF-alpha's activation of NFκB.

## PROTEIN SUPPLEMENTS:

Only very few recent randomized controlled trials have studied the effects of protein supplementation in clinical cachexia. It appears that supplementation of dietary protein (>1.5 g/kg per day) alone or in combination with other anabolic stimuli such as exercise training maintains or even improves muscle mass, but results on muscle function are controversial and no clinical studies have yet directly linked alterations in cellular signaling or metabolic signatures of protein intake-induced muscle anabolism to muscle weight gain.

The relative contribution of dietary protein intake in maintenance or accretion of muscle mass in the different stages of chronic wasting diseases remains unidentified and receives scarce attention in current clinical practice. Efficacy of dietary protein supplementation may not only depend on protein quantity and the specific amino acid formulation but also on the underlying

disease and clinical condition, as well as on presence of other intervention strategies targeted at muscle maintenance. These issues can only be addressed by a translational research approach including relevant in-vitro and in-vivo experimental models and controlled clinical trials with adequately phenotyped patients and appropriate outcome measures

**Optimal protein intake in cachexia**

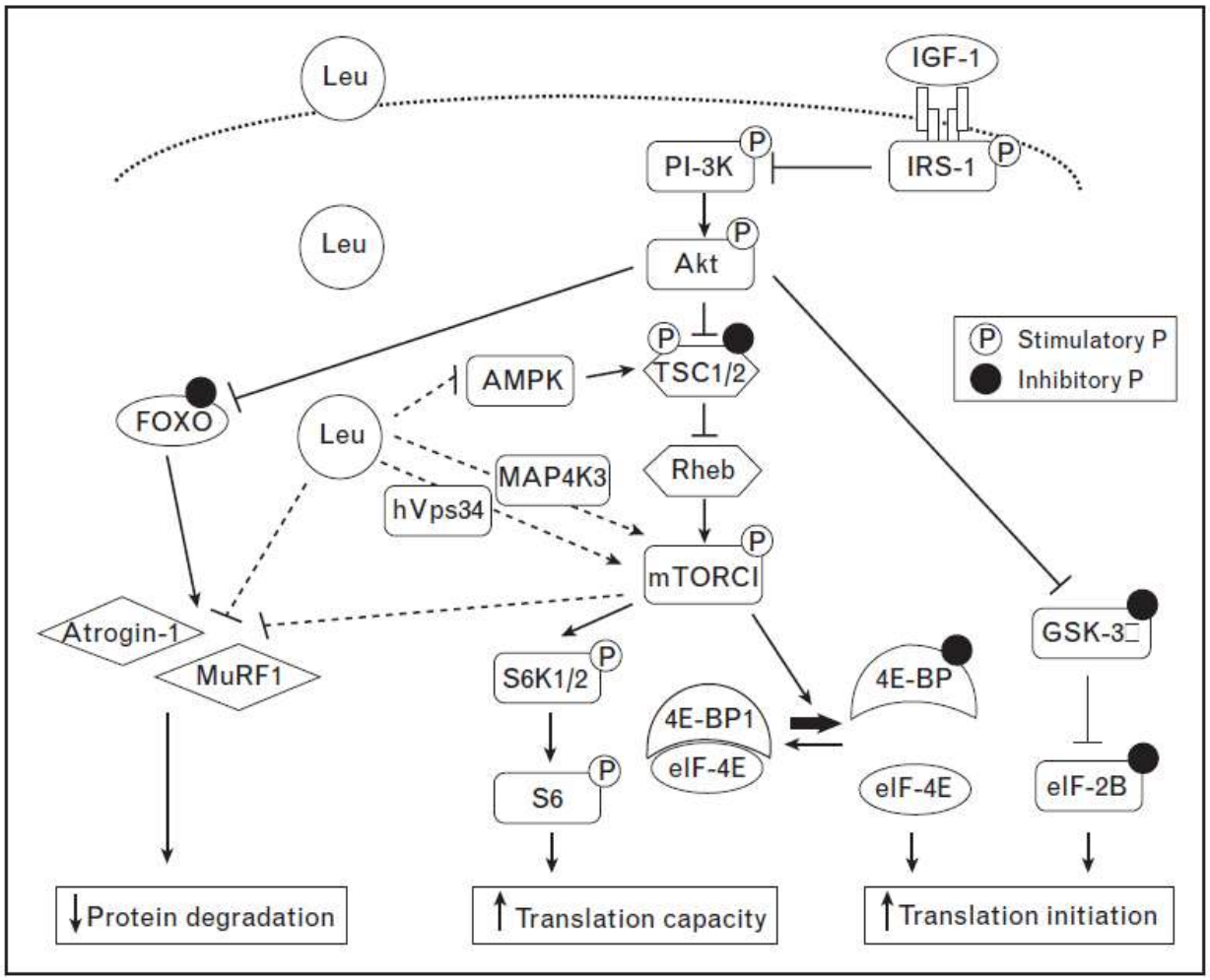
Maintenance of muscle is determined by the balance between muscle protein synthesis and breakdown, and therefore, to accomplish maintenance or even restoration of muscle mass in cachexia, maximal stimulation of protein synthesis and inhibition of degradation is desired. This requires optimal dietary protein intake, which may very well exceed the Recommended Dietary Allowance (RDA) of 0.8 grams (g) of protein per kilogram (kg) of body weight per day, the amount of protein that adequately maintains nitrogen balance in healthy individuals, including the elderly [2_]. Current estimations of protein requirements are mainly derived from studies on non-cachectic individuals, although some study populations shared characteristics of cachexia such as disuse. For instance, 45 g of essential amino acids per day, in addition to the RDA for protein, preserved muscle strength outcome during compulsory bed rest in elderly volunteers [3]. Optimal protein requirements are difficult to estimate as they may depend on the protocol, that is, higher values are obtained in short-term studies and estimates may be 40–50% higher using tracer methodology than using nitrogen balance studies [4]. Despite these difficulties and the possible variations in protein requirements in different diseases and clinical conditions, a minimum of 1.5 g/kg of body weight per day or 15–20% of total caloric intake appears justified for cachexia, considering that this amount was determined as optimal protein intake in sarcopenia [5_], which is also characterized by muscle depletion. Furthermore, experimental evidence and recent clinical studies indicate that in contrast to sarcopenia, in which a decreased muscle protein synthetic response has been identified, active cachexia is also characterized by increased muscle protein degradation [6,7]. For optimal dietary supplementation in cachexia, protein source and meal composition also need to be considered, as in the elderly, muscle protein synthesis was hypothesized to be blunted when protein and carbohydrate are coingested or when the quantity of protein is less than 20 g/meal [8]. Finally, timing of protein intake may be important in cachectic patients to avoid adverse effects of high protein intake on overall dietary intake in view of recently described dose-dependent satiating effects of protein in healthy volunteers [9].

**Regulation of muscle protein synthesis by dietary protein**

The regulation of muscle protein synthesis is very similar to that of other cell types, whereas some protein degradation routes unique to striated muscle have been identified. In nonpathological conditions, modulation of muscle protein turnover relies on the postprandial availability of nutrients like amino acids, which directly, and indirectly via the actions of or in combination with insulin, stimulate muscle protein synthesis and decrease degradation (Fig. 1). Anabolic effect of amino acids may partly be attributed to increased substrate availability; however, a mixture of the BCAAs or leucine alone stimulates protein synthesis to the same extent as a complete mixture of amino acids, indicative of a signaling role of these particular amino acids [21–23]. In contrast to protein synthesis signaling by insulin [24] or insulin-like growth factor-I (IGF-I) [25], these anabolic actions of BCAAs do not appear to be receptor-mediated [26], or require insulin receptor substrate (IRS-1) phosphatidylinositol- 3 kinase

(PI3K), and PKB/Akt activation. Subsequent signaling to increase protein synthesis by insulin/ IGF-I involves stimulation of mRNA translation via activation of eukaryotic initiation factors (eIFs) by inhibition of glycogen synthase kinase (GSK)-3 and activation of mammalian target of rapamycin (mTOR; reviewed in detail by Glass [25] and Proud [24]). Inhibition of GSK-3 abrogates its suppressive effect on eIF2B. Currently, there is no evidence to support regulation of GSK-3 activity by amino acids in the control of translation initiation. mTOR, on the other hand, is activated indirectly by Akt signaling – as this suppresses TSC1/ 2-inhibition of mTOR – resulting in increased activity of eukaryotic translation initiation factor 4E (eIF4E) as a consequence of the dissociation of eukaryotic translation initiation factor 4E binding protein 1 (4E-BP1) following mTOR-mediated phosphorylation. In addition to stimulatory effects on eIF activity, insulin/IGF-I signaling also promotes protein synthesis by increasing translation capacity and elongation. This occurs via phosphorylation of S6K1/2 and eIF-4E by the mTORC1 complex (Mtor associated with raptor and GbL) [27]. Supplementation of rats, which were starved for 18 h, with dietary protein results in decreased binding of 4E-BP1 to eIF4E [28], whereas long-term amino acid supplementation attenuated aging-induced decrease in muscle sarcomers [29_]. However, dietary protein supplementation does not always result in differences on muscle protein metabolism as is indicated by unchanged 13C-valine enrichment in muscle tissue [30], or muscle mass in tumorbearing mice [31_].

Leucine alone is sufficient to increase protein synthesis, which is mediated via the phosphorylation of 4E-BP1 and S6K1 as a result of phosphorylation and activation of mTOR in the mTORC1 complex. Of all amino acids, leucine appears the most potent stimulator of mTORC1 phosphorylation [22]. Glutamine even has inhibiting effects on mTORC1 signaling in cultured muscle cells [32,33]. The mechanism by which leucine stimulates mTORC1 phosphorylation is not fully understood, but human vacuolar protein sorting-34 (hVps34) and mitogenactivated protein kinase-3 (MAP4K3) have recently been described to be involved [34,35]. Leucine also stimulates protein synthesis by inhibiting adenosine monophosphate-activated protein kinase (AMPK)-mediated phosphorylation ofTSC2,which negatively controlsmTORC1, linking energy availability to mTORC1 signaling [23]. Indeed, supplementation of dietary leucine increased phosphorylation of mTOR, S6K1 and 4E-BP1 and formation of active eIF4E complex in 7-day-old piglets [36]. In contrast, addition of leucine had no effect on muscle or carcass weight in cachectic mice [31]. This could be explained by the recent finding that dietary leucine influences peak activation but not duration of skeletal muscle protein synthesis and mTOR activation [37]. Discrepancies between anabolic signaling signatures and muscle maintenance have also been described in weight stable COPD patients with muscle atrophy, as increased phosphorylation of Akt and downstream mediators (i.e., 4E-BP1, S6K1 and GSK-3b) were explained as a failed attempt to maintain muscle mass [38].




AMPK, adenosine monophosphate-activated protein kinase; eIF, eukaryotic initiation factor; GSK, glycogen synthase kinase; IGF, insulin-like growth factor; IRS, insulin receptor substrate; mTOR, mammalian target of rapamycin.

## AMINO ACID LOADING

Even small changes in protein synthesis or protein degradation lead to large protein deficits because the rate of protein turnover for humans is high (240–310 g/day).21 As previously outlined, there are currently no standardized means of minimizing the loss of skeletal muscle in CIC beyond aggressive treatment of the underlying illness and the experimental therapies described within. The loss of skeletal muscle in CIC is often coupled with patient fatigue/weakness from chemotherapy or radiation. Disuse of a muscle for even two weeks can result in reduction of its size by 20%. Cxl

Logically, maintenance of skeletal muscle would require available amino acids as protein synthesis is stimulated only in the presence of available precursors, such as branched chain amino acids, leucine, and the appropriate hormonal milieu.cxli Many patients have been encouraged to increase their protein intake above the recommended daily allowance (RDA) of

0.8g/Kg/day for adults older than 19.cxlii Commercially available liquid supplements such as Boost® and Ensure® also offer high protein options. In-vivo data has supported the use of amino acid loading in an effort to support muscle synthesis by ensuring a constant supply of amino-acid precursors however in-vivo data has been conflicting. A phase III trial with over 400 advanced stage cancer patients with up to 10% weight loss randomized patients to receive an amino acid compound containing beta-hydroxl beta-methyl butyrate, glutamine, and arginine (HMB/Arg/Gin) or placebo (RTOG 0122). The amino acid mixture was taken twice daily for eight weeks and lean body mass was measured using bioimpedence and skinfold measurements. 37% of enrolled patients completed the protocol with attrition due to patient preference. Using an intention to treat analysis, there was no significant difference in the 8-week lean body mass between the two arms. Cxliii

Another parenteral branched amino acid product, Aminoleban®, has been used for patients with protein malnutrition resulting from liver cirrhosis. Meng et al. completed a prospective randomized controlled trial with fifty patients with hepatocellular carcinoma and a history of cirrhosis. After hepatic resection, patients were randomized to receive Aminoleban®, or an isonitrogenous, isocaloric placebo. There was no difference in morbidity or mortality in the post-operative period, however the study group did have improved liver function with higher albumin and lower bilirubin levels.cxliv One study evaluated the impact of dietary supplementation with a combination of high protein, leucine, and fish oil in tumor-bearing cachectic mice. The mice were divided into weight-matched groups: 1) control, 2) mice with adenocarcinoma, 3) mice with adenocarcinoma receiving the combination supplement. Mice with adenocarcinoma showed reduced muscle and fat mass as expected. Mice with adenocarcinoma receiving the combination supplement showed significantly reduced muscle and fat loss and improved muscle performance. In addition, 24-hour activity was assessed and the experimental mice had increased performance.cxlv While data remains conflicting in hum ans, many oncologic nutritionists and practitioners continue to recommend increased protein intake for patients experiencing CIC based on the strong in-vitro data and known muscle synthesis processes.

**Trials with proteins and other dietary supplements**

In a randomized controlled study of 32 cachectic advanced solid tumours (stage IV) patients from several types of cancer such as colon, ovarian, lung, pancreatic, and other cancer, May et al. tested a combination of β-hydroxy-β- methylbutyrate (HMB), arginine, and glutamine and showed an overall benefit with an increase in lean body mass (LBM), improved mood, less weakness, and improved haematological parameters after 4 weeks compared with placebo21 (Table 3). A mixture of HMB, glutamine, and arginine or an isonitrogenous, isocaloric control was supplemented in 472 advanced lung and other cancer patients. However, there was no statistically significant difference in the 8week LBM between the two arms.22 Seventy-two participants with advanced pancreatic cancer taking L-carnitine showed an increase in body mass index (BMI) by 3.4 ± 1.4%; a decrease in BMI was observed in the control group. There was also a trend towards an increased overall survival in the L-carnitine group and reduced hospital-stay.15 In another controlled trial, 332 patients were randomized into five treatment arms, comparing megesterol, eicosapentaenoic acid, carnitine, and thalidomide with a combination of all four substances in the fifth arm.14 An analysis of pre-treatment to posttreatment changes showed that LBM significantly increased, while the resting energy expenditure decreased in the combination arm. Thus, study findings revealed that the combined supplementation was superior.

Carnitine alone did not show any benefits. In a small study of nine malnourished participants with intra-abdominal cancer, participants received both conventional total parenteral nutrition (TPN) containing 19% branched-chain amino acids (BCAA) and isocaloric, isonitrogenous TPN containing 50% BCAA (BCAA-TPN).24 The trial showed that the fractional albumin synthesis rate increased significantly on daily BCAA-TPN. Another study from Tayek et al. investigated the effect of a BCAA-enriched solution in 10 malnourished patients with intra-abdominal metastatic adenocarcinoma.25 The participants were given isonitrogenous amounts of both a conventional (TPN) formul a containing 19% BCAA and a BCAA-enriched TPN formula containing 50% of the amino acids as BCAA in a random order. BCAA-enriched formulae group showed significant increases in whole body protein synthesis and leucine balance. Both studies demonstrated potential clinical benefits associated with BCAA-enriched TPN in cancer cachexia patients.

Supplementation with combinations of antioxidants, vitamins, omega-3 fatty acids, medroxyprogesterone acetate, and celecoxib23 was used in a study of 39 cancer patients. The study reported positive effects stabilizing or increasing weight, LBM, and appetite. In another study, an Ethanwell/Ethanzyme (EE) regimen was investigated in 68 malnourished patients with head and neck cancer.26 Ethanwell is a protein-dense and energy-dense oral nutritional supplement that contains several ingredients including omega-3 fatty acids, glutamine, selenium, and CoQ10. Ethanzyme is an enzyme product composed of multiple probiotics and vitamins. The result showed that an EE regimen improved body weight as well as serum albumin and prealbumin levels in head and neck cancer patients with a BMI <19. However, methodology in both abovementioned studies did not allow to differentiate the beneficial effects of the individual substances in the combination therapies.

**Adverse effects with dietary supplements**

Adverse effects were metallic taste after magnesium supplementation, 17 diarrhoea,14,15 and nausea15 after L-carnitine supplementation, or mild abdominal discomfort and transient diarrhoea after a mixture of omega-3 polyunsaturated fatty acids plus vitamin E.20 HMB in combination with arginine was associated with nausea, constipation, and diarrhoea. 22 EE regimen26 led to oral mucositis and emesis. Arginine in combination with omega-3 fatty acids and/or RNA27,34,35 was associated with abdominal cramping, bloating, diarrhoea, nausea, and vomiting.

## Biochemical Markers

***Protein Status* ( *Serum Albumin , Prealbumin , and Transferrin* )**

Serum hepatic protein (albumin, transferrin, and prealbumin) levels have historically been linked to nutritional status. Nutritional status and protein intake are the signifi cant correlates with serum hepatic protein levels. Evidence has consistently suggested that serum hepatic protein levels correlate with morbidity and mortality and thus are useful indicators of severity of illness. Although serum hepatic proteins do not measure nutritional repletion (with the exception of prealbumin), it has been shown to be useful in identifying those who are the most likely to develop malnutrition, even if well nourished prior to onset of illness [ 61 ] . Serum proteins provide indirect information about visceral protein levels, indicating less hepatic synthesis which is usually a consequence of intake defi - cits. In cancer patients who are provided nutrition

therapy including proteinsparing diets supplemented with proteins, an increase in serum hepatic proteins could signify an anabolic response. With half-lives of prealbumin (2–3 days) and serum transferrin (8 days) being relatively much shorter compared to serum albumin (15–20 days), changes in response to nutritional therapy can be observed within days of repletion [ 62 ] . Serum prealbumin and transferrin are thus considered relatively more sensitive parameters of the effi cacy on nutrition interventions.

***Serum albumin*** is the most validated as a prognostic index and readily available biochemical parameter used to assess protein status. However, its relatively long half-life (14–20 days) makes it slow to respond to dietary interventions. Since the intervention period is  12 weeks, we have selected this to measure change in visceral protein stores. Perioperative serum albumin has also been observed to predict prognosis and survival in colorectal cancer patients undergoing surgical treatment [ 63 ] . In a comprehensive review of epidemiological data investigating the prognostic value of serum pretreatment albumin levels and survival in a heterogenous group of cancers, Gupta and Lis [ 8 ] demonstrated the this was an excellent prognostic marker and may be used to better defi ne baseline nutritional risk in cancer patients. Marin Caro et al. [ 3 ] observed a signifi cant association between patients with low serum albumin levels and nutritional intake.

***Prealbumin*** changes to short-term interventions are best indicated by prealbumin since it has a 2-day half-life versus albumin, making it a good indicator for early monitoring. Prealbumin is also unaffected by hydration status and, together with transferrin, predictive of changes in serum albumin [ 62, 64 ] . Prealbumin levels may be reduced with hepatic dysfunction, acute catabolic stress, sepsis, surgery, trauma, or severe enteritis or ulcers which may result from cancer treatment or progression of disease versus inadequate intake.

***Transferrin*** is a serum beta globulin protein synthesized primarily in the liver, but unlike albumin it is located intravascularly as a transporter of iron, has a shorter half-life (8–10 days), and responds more rapidly to changes in protein status. Although transferrin levels are affected by iron status, serum transferrin, either singly or as part of a multiparameter index, is the *strongest predictor of cancer patient mortality and morbidity* [ 62, 64, 65 ] . Serum transferrin receptor is a marker of severe iron defi ciency only when iron stores are exhausted. Clinical studies indicate that serum transferrin is less affected by infl ammation [ 65 ] . The limitation of using transferrin as an indicator of nutritional status in cancer patients is that serum levels will decrease in chronic infections, acute catabolic states, surgery, and with renal impairment. It may be important to recognize the challenge that patients with a syndrome like cachexia or with multiple, confounding symptom clusters may have inconsistencies in hepatic protein levels. Other potential confounding factors include stage of disease and impact of prospective concurrent anticancer therapies including surgery, chemotherapy, and radiation therapy. There is substantial evidence of the correlation between serum hepatic proteins and infl ammation, making these the most relevant biomarkers in CC. Serum transferrin, prealbumin, and albumin have been observed as intermediate endp oint biomarkers and independently associated with worse outcome in cachexia [ 66, 67 ] . Measurements of body composition combined with more objective and sensitive measure of protein nutriture is ideal for the biochemical assessment of intravascular and visceral protein stores. Over 70% of patients of both genders with advanced cancer receiving palliative care have been shown to consistently have below normal serum hepatic protein levels [ 30 ] . Plasma levels of proteins (prealbumin, albumin, and transferrin)

have been consistently used as indicators of protein-calorie malnutrition in the general population.

**Protein**

Injury and illness are known to produce marked losses of protein as indicated by increases in urinary nitrogen excretion [ 89 ] . Acceleration of protein turnover and derangements in protein metabolism have also been seen in cancer patients [ 96 ] . Protein-calorie defi cits have been shown to contribute to malnutrition in esophageal cancer patients. Provision of exogenous energy and protein has been shown to invoke an anabolic response as indicated by an increase in serum prealbumin and transferrin level in this patient population [ 62 ] . In contrast to simple starvation where the body attempts to spare protein, the opposite is true under conditions of metabolic stress such as the cancer process itself or combined with antineoplastic therapy. The most accurate method of determining protein requirements in a hypermetabolic patient is based on urinary nitrogen loss; however, this is impractical in most settings due to the labor intensity involved in collecting 24-h urine specimens and fecal specimens for total nitrogen output in addition to accurately calculating protein intake. The only setting in which this might be feasible is in critical care.

The estimated protein requirement is determined based on the degree of protein depletion and the metabolic stress factors. For the well-nourished, mildly stressed individual, the protein needs may only be 0.8–1.0 g/kg IBW ; however, with mild to moderate depletion combined with metabolic stress, 1.5–2.0 g/kg IBW may be required to achieve positive nitrogen balance and protein repletion. Another method of estimating protein requirements is by calculating the ratio of nitrogen to nonprotein calories. It is recommended to provide 1 g nitrogen (protein in grams divided by 6.25) per 120–150 nonprotein calories for anabolism in the moderately to severely malnourished or stressed patient [ 97, 98 ] . As with estimating calorie requirements, the best indicator of whether protein needs are being met is with monitoring and reassessment for weight gain and nitrogen retention in the malnourished patient and weight maintenance and nitrogen equilibrium in the wellnourished patient [ 99 ] . Initially, the pathophysiology of CC had two principle components – a failure of food intake and a systemic ypermetabolism/hypercatabolism syndrome. Additionally, diets adequate in calories from fats and carbohydrates were required in “protein-sparing” quantities for muscle anabolism [ 100 ] . Protein intake must also be suffi cient for wound repair, resistance to infection, and synthesis of enzymes and plasma proteins [ 101, 102 ] . Supplementation with glutamine, arginine, and branched-cha in amino acids appears to support improvement in reducing complications and improving treatment outcomes [ 103 ] .

Future clinical trials should evaluate the impact of multimodal interventions using, in addition to nutrients and appetite stimulants, immune modulatory nutrients for the treatment of malnutrition in well-powered clinical trials. Guidelines for estimating protein requirements are provided in Table 2.5 . However, as with total calories, these calculations are an estimate and not based on actual measurement of protein expenditure in cancer patient populations. Thus, the best indicator of adequacy is the patient’s response to the nutrition regimen. Monitoring of patient progress and adjustments of protein intake goals as needed are essential parts or the nutrition care plan.

**Calculating protein requirements**

For calculating protein needs :Divide IBW by 2.2 = kg of IBW

For protein maintenance :Multiply 0.8 −1.4× kg of IBW
For protein anabolism:Multiply 1.5× kg of IBW

**BENEFITS OFWHEY PROTEIN**

Whey protein is considered as an excellent protein for the choice of individuals of all ages for healthy diet and also to improve and maintain their health. Traditionally, Whey protein was only used by most of the athletes and bodybuilders to promote the muscle growth [2]. But from past few years, whey protein is being used in some other applications.

Some applications that using whey proteins are: cancer treatment, wound healing, infant health and weight loss. According to Hoffman and Falvo [4], additional benefits of Whey protein may include: Whey protein helps to increase the serotonin activity and helps to promote restful sleep [10]; Whey protein helps enhance energy levels; it helps to decrease the stress; it helps to keep the metabolic rate high; it helps to reduce body fat and build the lean body mass; and it helps to improve the memory loss under stress. In addition to these, some of the top benefits of whey protein may include: it provides immunity support, increase muscle mass, boost metabolism, and helps to improve overall health [7].

Whey proteins promote:
· Muscle strength
· Improved immune system
· Muscle synthesis
· Performance / endurance
· More favorable body composition
· Recovery

Cancer patients are undergoing chemotherapy or radiation may have difficulty in meeting their nutritional requirements and this is because of lack of appetite. So, this may lead to muscle loss, weight loss and protein calorie malnutrition. Here, the use of whey protein provides excellent protein choice for the cancer patients [13]. In addition to these, it helps them very easy to digest.

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