Pathophysiology of Cachexia in the Elderly

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Introduction

The physiological decline in food intake that occurs with aging is an appropriate response to the reduced physical activity of this population. This physiological decline is termed the 'anorexia of aging' [1]; however, cachexia in the elderly seems to be reaching epidemic levels, with 30–40% of men and women over age 75 being 10% underweight or more [2]. There is no agreed upon definition for cachexia, which means 'poor condition' in Greek [3]. While it has traditionally been thought that chronic illness fully explains the pathogenesis of cachexia, this concept is proving inadequate [4]. In general, cachexia is characterised by weight loss due to loss of fat and skeletal muscle mass [5].

Many chronic illnesses can be associated with cachexia, although the condition may develop in older people without obvious disease [3]. Starvation is different from cachexia in the sense that macronutrient changes can be reversed by feeding in starvation but not in cachexia. There are four major causes of weight loss in older persons: starvation, sarcopenia, cachexia and dehydration (Table 1).

Regulation of Appetite in the Elderly

Regulation of appetite is a sophisticated process that involves feedback from peripheral sensory endings and the interaction of a variety of neurotransmitters in the central nervous system [1]. Numerous studies have shown that food intake declines over the human lifespan, with males having a greater decrease in food intake than females. A large part of the anorexia of aging seems to be related to the changes in gastrointestinal activity that occurs with aging [1].

During a meal, the fundus distends to accommodate food, a process termed adaptive relaxation. Food is then passed to the antrum after mixing with stomach secretions. Antral distension is the major signal for termination of a meal [1]. With aging, there appears to be impaired gastric fundal accommodation [6] due to impaired adaptive relaxation, which is caused by a decline in the local release of nitric oxide. Older mice have decreased nitric oxide synthase activity in their fundus [7]. The decline in adaptive relaxation that occurs with aging leads to more rapid antral filling. In addition, some studies suggested that large-

Table 1. Comparison of the major features of starvation, sarcopenia, cachexia and dehydration

	Starvation (Anorexia of aging)	Sarcopenia	Cachexia	Dehydration
Weight loss	++	+	+++	++
Loss of lean mass	+	+	+++	0
Loss of fat mass	++	0	++	0
Cytokine excess	+/-	+	+++	0
Albumin	_	0	__	0
Anaemia	+/-	0	++	0
Hypogonadism	+/-	+	++	0

volume solid meals delay the rate of gastric emptying in the elderly [8–11]. This will eventually lead to prolongation of antral distension, which results in satiety (Fig. 1).

Infusion of lipid into the duodenum leads to the release of the peptide hormone cholecystokinin (CCK), which, in turn, leads to satiety. Evidence from animal studies indicates that CCK suppresses appetite in older animals more than in younger animals [12, 13]. This finding was also confirmed in humans. In addition, the basal circulating concentration of CCK and its response to lipids increases with aging, mainly due to a decline in the CCK clearance rate. CCK exerts its effects by increasing contractile activity in the pylorus, leading to slowing of gastric emptying and increasing the antral response to gastric distension [14]. CCK also directly stimulates the ascending vagal fibres that carry satiating signals to the nucleus tractus solitarii and to the hypothalamus [15].

Glucagon-like peptide is another gastrointestinal hormone involved with satiation, but its levels do not change with aging [16]. In contrast, amylin levels, which in mice decreases food intake in young and old mice, increase from middle age to old age [17].

The hormone leptin is released from adipose tissue [18] and exerts its effects by decreasing food intake and increasing the metabolic rate. Circulating leptin levels increase in older men and decrease in older women [19]. The increase in leptin levels in men is related to the decrease in testosterone that occurs with aging [1], which, in turn, is associated with muscle loss [20] and an increase in body fat [21]. Testosterone replacement in older men leads to a decline in leptin levels [1]. The increase in leptin with aging in men is considered a major factor in the increased anorexia of aging that occurs in males compared to females.

Although animal studies suggest that a decline

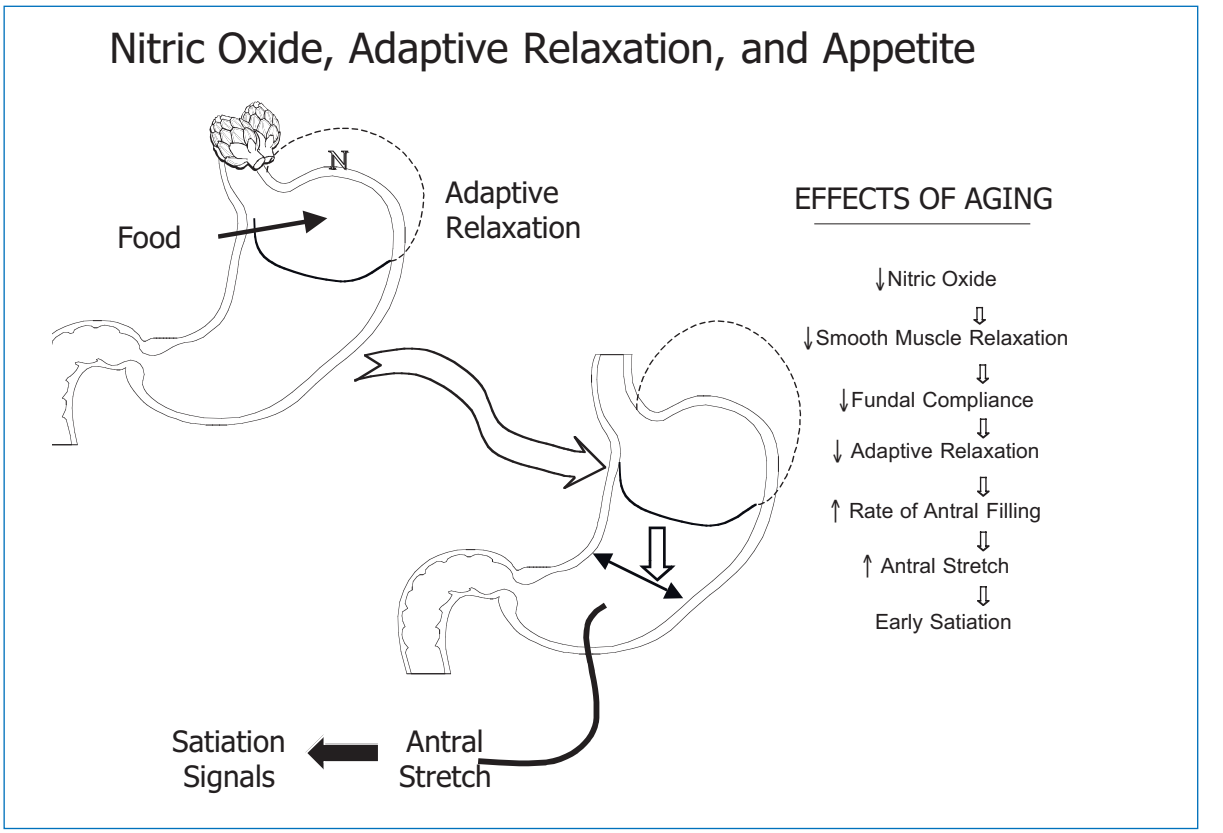

Fig. 1. Alterations in stomach motility that lead to the anorexia of aging

in opioid activity in the central nervous system may be associated with anorexia in older animals [22, 23], a study in humans did not show any difference in the effect of naloxone on food intake [12]. In humans, alteration in the thirst drive, which is modulated by μ-opioid receptors, appears to play a role in the development of age-related hypodipsia. Similarly, numerous neurotransmitters, such as neuropeptide Y, norepinephrine, and serotonin are involved in appetite regulation, although their role in the pathogenesis of the anorexia of the aging has been poorly investigated. An excess of corticotropin releasing factor is thought to be involved in the pathogenesis of the severe anorexia associated with depression in older persons.

Factors Leading to Reduced Food Intake in the Elderly

Hedonic Qualities of Food

As a general rule, aging is associated with decreased appreciation of the hedonic qualities of food [24]. This change seems to be caused more by alterations in olfaction than in taste. There is a marked decline in odour detection and taste thresholds increase with aging. However, these changes are minor unless the person smokes, is on medications, or has zinc deficiency. Older persons tend to prefer more intense flavours than do younger persons [25]. For example, it was shown that elderly persons had an increase in food intake when the flavour was enhanced with monosodium glutamate [26].

Social Factors

Studies have shown that elderly persons consume more food when eating a meal in the company of others [27, 28]. The explanation for this, in part, is that eating in company results in spending a longer time eating the meal. In nursing homes, several factors can lead to malnutrition and cachexia in the elderly, including the reduced variability of food, the complicated process of food preparation and distribution, and inadequate attention by caretakers to the individual needs of each of the patients [24]. Retirement can lead to reduced household income and thus to insecurity about buying food and then to weight loss [29]. Moreover, retirement can also lead to social isolation, changes in life style, and loss of contacts. All of these add up to the risk of weight loss and cachexia following retirement. Simple changes, such as the expansion of commercial shopping areas, the erection of high-rise apartments, or the increasing diversity of the neighbourhood, may elicit a strong sense of insecurity within an environment the older adult previously perceived as safe [29].

Psychological Factors

Depression and dementia interact to accelerate weight loss [24]. Depression has been shown to be the major cause of weight loss in community and institutional settings [30], while demented patients lose weight due to failure to eat – although some demented patients may increase their energy expenditure by wandering. Some persons with cognitive impairment develop apraxia of eating. Other factors that may contribute to the development of weight loss in demented patients are difficulty swallowing, dental diseases, lack of concern about eating, and memory loss. In demented patients, disturbance of the mechanisms for appetite regulation may lead to hypo- or hyperphagia. The latter usually occurs early in the course of the dementing process.

Medical Factors

Although dentition was always mentioned as a factor leading to reduced food intake, studies did not confirm that poor dental health makes older patients prefer food of softer consistency [31]. However, poor dentition does lead to a slight decrease in daily food intake. Chronic diseases, some of which are common in older people, have been shown to produce anorexia and cachexia: these include cancers, AIDS, rheumatologic diseases, end-stage renal disease, chronic obstructive pulmonary disease, and heart failure. The most common reversible causes of weight loss are given in Table 2.

Drugs have also been implicated to cause reduced food intake and cachexia, by causing either a taste complaint or nausea and vomiting. Among the drugs with these possible complications are antihypertensives, diuretics, sleeping pills, and nonsteroidal anti-inflammatory agents.

Table 2. Reversible causes of weight loss

Social:
Loneliness
Problems in shopping
Problems in food preparation
Poverty
Elderly abuse
Psychological:
Depression
Late-life paranoia
'Cholesterol' phobia
Alcoholism
Anorexia tardive
Medical:
Decreased food intake:
- Iatrogenic
- Medications
- Therapeutic diets
- Altered food consistency
Dysphagia
Dentition problems
Addison's disease
Hypercalcaemia
Some cancers
Malabsorption
Diarrhoea, e.g. caused by *Clostridium difficile*
Gluten enteropathy
Bacterial overgrowth
Pancreatic insufficiency
Hypermetabolism
Hyperthyroidism
Phaeochromocytoma
Essential tremor
Diabetes mellitus

Sarcopenia

Sarcopenia is severe age-associated loss of muscle mass that causes limitations in activities of daily living and an increased mortality in affected persons, especially those who have obese sarcopenia (the 'fat frail').

The causes of sarcopenia are multifactorial (Table 3). Aging itself is associated with a decline in physical activity. Small increases in cytokines, especially interleukin (IL)-6, have been implicated in the proteolysis of muscle involved in the pathophysiology of sarcopenia [32]. Decreased food intake can lead to loss of muscle protein, as it is broken down for use in more essential proteins. The amino acid creatine is found only in meat and is essential for muscle function. Older persons who are anorectic or vegetarian have inadequate creatine intake for muscle maintenance.

With aging, testosterone levels decrease because of failure of the hypothalamic-pituitary-gonadal axis [33]. The decline in testosterone occurs at the rate of about 1% per year, beginning at 30 years of age. Loss of testosterone leads to an increase in adipocyte precursors and a decrease in satellite precursors. In addition, it is associated with a decline in muscle-protein synthesis. Testosterone replacement in older persons increases muscle mass and, to a lesser degree, muscle strength [34].

Myostatin is a protein that blocks muscle synthesis. Mice made transgenic for myostatin have a marked decrease in muscle mass, mimicking cachexia [35]. Recently, a human with a double deletion of the myostatin gene was reported to have muscle hypertrophy [36].

Table 3. Causes of sarcopenia

Aging
Physical inactivity
Anorexia
Decreased creatine intake
Peripheral vascular disease
Hypogonadism
Cytokine excess
Myostatin excess

A final cause of sarcopenia is atherosclerosis, which causes peripheral vascular disease. This is associated with decreased muscle mass and strength in the lower extremities, as well as decreased mobility.

Cachexia Pathophysiology

Cachexia in the elderly cannot be completely explained by reduced food intake; rather, several social and psychological factors, disease conditions, and medications can aggravate the physiological anorexia of aging and lead to weight loss [1]. Furthermore, a person eats less when he or she eats alone compared to when eating in a group. The pleasurable qualities of food are determined by taste, smell, and vision [1], with olfaction being the most important determinant [1]. The decreased sense of smell and the changes in taste that occur with aging (taste threshold, difficulty in recognising taste mixtures, and increased perception of irritating tastes) contribute to anorexia [1]. Other factors that contribute to the development of cachexia are detailed in the following sections.

Cytokines

The immune system, particularly inflammatory cytokines, has a crucial role in cachexia (Fig. 2). Cytokines are the cause of inflammatory reactions in disease states, and the most important contributor to this process is tumour necrosis factor (TNF). TNF, together with IL-1, IL-6, and interferon (IFN)-γ regulate apoptosis, which may mediate cachexia associated with chronic disease states.

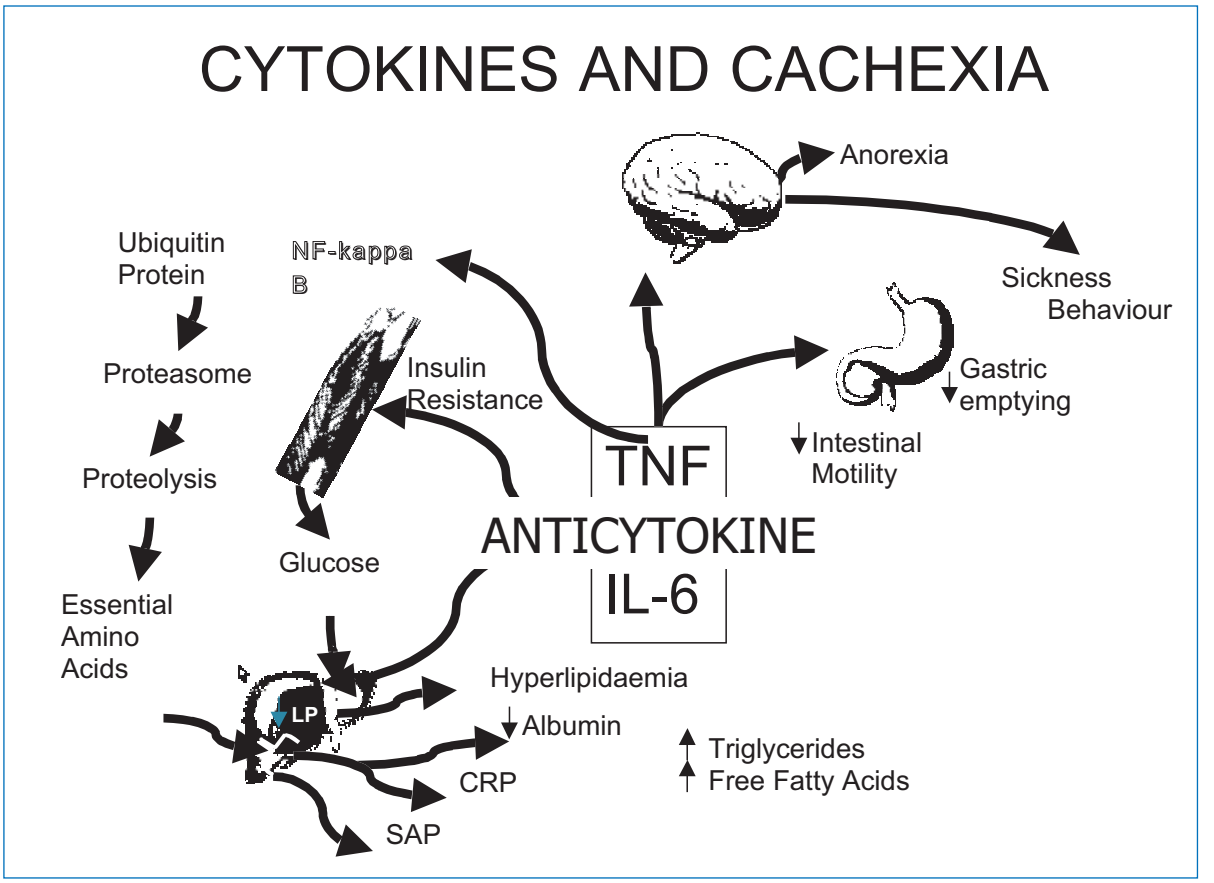

Fig. 2. Pathophysiology of cachexia. *IL-6*, interleukin-6; *TNF*, tumour necrosis factor; *CRP*, C-reactive protein; *SAP*, serum amyloid protein; *NF-kappaB*, nuclear factor–kappaB

Studies have shown an increased concentration of cytokines in the circulation of patients with cachexia. In cancer patients, for example, the patient's clinical status determines the serum level of TNF-α. In a study of 91 patients with B-cell chronic lymphocytic leukaemia, serum levels of TNF-α were high in all stages of the disease, with a progressive increase in relation to the stage [37]. It was also found that TNF-α levels were higher in patients with endometrial carcinoma than in healthy postmenopausal women or women with endometrial hyperplasia. In addition, TNF-α levels increased with advancing stage of the disease [38].

Other studies have shown that cytokines are able to induce the metabolic changes typically associated with cachexia, such as stimulating muscle proteolysis through the ubiquitin-proteasome pathway, or inhibiting lipoprotein lipase, which is responsible for mobilising triglycerides from the circulation into adipocytes [39]. Cytokines in general exert their effect by crossing the blood-brain barrier and stimulating ascending fibres in the vagus. Cytokines cause anorexia and muscle wasting, as well as decreased nitrogen retention, anaemia, decreased albumin synthesis, and extravasation of albumin from the intravascular space [1]. An excess of cytokines is commonly detected in frail older persons [1].

Tumour Necrosis Factor

TNF-α is a 17-kDa peptide that is largely produced by the monocyte/macrophage cell line. Other cells, including T-cells, NK cells, mast cells, and adipocytes, also produce this cytokine. Production of TNF-α is synergistically regulated by other cytokines, such as IL-1 and IFN-γ [39], and TNF-α in turn stimulates leptin and IL-6 production [1]. Studies have shown that injecting rats with recombinant human TNF-α led to significant depletion of body protein. It was also demonstrated that injection of TNF-α directly into the cerebral ventricles of rats suppressed food and water intake, while peripheral administration of an equal or higher dose had no such effect [39]. While TNF-α failed to produce a sustained weight loss, the net metabolic alterations exerted by the cytokine may depend on the site of production [40]. This was demonstrated by intracerebral injection of TNF-α-secreting cells, which resulted in body weight loss and anorexia, while TNF-α-producing cells inoculated into peripheral tissue triggered cachexia, including weight loss, depletion of lipid and protein stores, and anaemia but without significant anorexia [39, 40].

Short intravenous infusion of recombinant human TNF-α increased plasma triglyceride levels, and glycerol turnover by more than 80%, free fatty acid turnover by more than 60%, and protein turnover. Those changes resolved with continuous administration [5].

Some evidence suggests that treatment of patients who have tumours or infections with antibody directed against TNF-α attenuates the wasting syndrome [39]. In another study, administration of anti-murine-TNF-α antibody to rats carrying the Yoshida AH-130 ascites hepatoma slowed the rates of protein degradation in skeletal muscle and liver, but did not affect weight loss [5].

Interleukin-6

Interleukin-6 has been called the 'geriatric cytokine,' and there is evidence from animal studies supporting a role for IL-6 in the development of cancer cachexia [5, 41–43]. Those studies, based on a murine colon-26 adenocarcinoma model [41–43], showed that administration of anti-mouse-IL-6 monoclonal antibody blocked the development in mice of weight loss and other parameters of cachexia [5, 41–43].

It seems that IL-6 is able to induce cachexia by several mechanisms, including triggering of the acute-phase response [5], inhibiting the activity of lipoprotein lipase in adipose tissue in mice [5], and inducing muscle atrophy in IL-6 transgenic mice [5]. Further evidence for the role of IL-6 in the development of cachexia comes from the findings of Strassman et al., who reported that IL-1-dependent IL-6 production was responsible for adenocarcinoma-associated cachexia [44]. Other studies used two subclones of the murine colon 26 adenocarcinoma cell line, clone 20, which is cachexigenic, and clone 5, which is non-cachexi-

genic. Possible involvement of IL-6 in the development of cachexia was suggested by the finding of increased serum levels of biologically active IL-6 in mice carrying clone 20, but not in those carrying clone 5 [42, 45, 46]. The injection of anti-IL-6 antibody partially inhibited the weight loss caused by inoculation of clone 20, suggesting that IL-6 is necessary, but not sufficient, for the development of cachexia [47].

Muscle atrophy in IL-6 transgenic mice was totally blocked by antibody to the mouse IL-6 receptor [48]. IL-6 administration to rats acutely activated total and myofibrillar protein degradation in skeletal muscles [49]. In another study, it was suggested that IL-6 up-regulates pathways of protein degradation [50]. It was also demonstrated that weight-losing patients with non-small-cell lung cancer had statistically significant increases in IL-6 and C-reactive protein, which was not the case in patients with the same tumour but without weight loss [5, 51].

Interleukin-1

Interleukin-1 is an inflammatory cytokine that has biological activity similar to that of TNF-α. It is mainly produced by macrophages and endothelial cells, and is known to be a pyrogen and a potent trigger of the acute-phase response. IL-1 suppresses lipoprotein lipase and stimulates intracellular lipolysis. Administration of recombinant IL-1 induces anorexia, weight loss, hypoalbuminaemia, and elevated amyloid P levels in mice [52]. In one study, it was observed that IL-1 administration to rats led to accelerated peripheral protein loss with preservation of liver protein [53]. However, administration of an IL-1-receptor antagonist to rats bearing the Yoshida ascites hepatoma was ineffective in preventing tissue depletion and protein degradation [54], and transfection of a cachectic tumour cell line (colon 26) with the gene for IL-1 receptor antagonist failed to stop tumour-induced cachexia [46]. In general, the mechanism by which IL-1 can produce cachexia is thought to be either an effect on hepatocytes, with a subsequent effect on the hypothalamic appetite centre [55], or a direct effect on the central nervous system [46, 57–60].

Interferon-γ

IFN-γ is secreted by activated T-cells and NK cells. Immunologically, it is the most potent monocyte-macrophage activating factor [39]. The metabolic effects of IFN-γ include inhibition of lipoprotein lipase, both in an adipocyte cell line and in vivo [61]. IFN-γ also inhibits the production of lipoprotein lipase and glycerol-phosphate dehydrogenase, both of which are involved in lipogenesis in primary cultures of rat adipocytes [62]. In addition, IFN-γ stimulates lipolysis in vitro and in vivo [63].

It was shown that a potentially lethal cachexia developed in nude mice inoculated with Chinese hamster ovary (CHO) cells overexpressing the mouse IFN-γ gene [64]. The mice developed weight loss, fat-store atrophy, and reduced food intake [39], which were predominantly due to effects not related to a decline in food intake. In addition, the degree of cachexia was proportional to the number of IFN-γ-producing cells and was blocked by pretreatment of the mice with anti-IFN-γ antibodies [39]. Mice bearing Lewis lung tumours developed a similar condition [65]. In that model, treatment with anti-IFN-γ antibody exerted anti-cachectic effects, partially through antagonising tumour growth. In addition, even after its effect on tumour growth had diminished, the antibody continued to have anti-cachectic properties.

Another study supporting the role of IFN-γ in cachexia compared the effects of anti-IFN-γ and anti-TNF-α antibodies on cachexia in rats bearing methylcholantrene-induced tumours [66]. The conclusion was that endogenous IFN-γ production is more crucial than that of TNF-α in the development of cachexia.

Leukaemia Inhibitory Factor

A role was suggested for LIF in the development of cancer cachexia, due to its ability to decrease lipoprotein lipase activity. LIF mRNA was shown to be present in two types of melanoma xenografts that induced weight loss in transplanted animals, whereas none was detected in non-cachexia-inducing xenografts [5, 67]. It seems unlikely that inhibition of lipoprotein lipase alone

could account for fat-cell depletion, and there is no mechanism to explain the catabolism of skeletal muscle.

Lipid Mobilising Factors

Almost all of the evidence behind a role for lipid mobilising factors (LMFs) in cachexia is derived from tumour studies. LMFs exert their effects on adipose tissue, leading to the release of free fatty acids and glycerol. There is evidence that tumours produce an LMF, as demonstrated in a study in which nonviable preparations of Krebs-2 carcinoma, when injected into mice, were able to induce the early, rapid stage of fat depletion [5]. More evidence for the presence of an LMF was provided by the finding that ascites serum from rats transplanted with the Walker 256 carcinoma stimulated lipolysis in an in vitro assay [68]. In addition, injecting serum from mice bearing a thymic lymphoma into controls produced fat loss [69]. The factor presumed to induce fat loss was found in tumour extracts, in the sera of patients with adenocarcinomas of the cervix and stomach, and in tissue-culture medium [5]. Together, those results led to the proposal that LMF was tumour-derived and released into the circulation. Other studies showed that the concentration of LMF in the sera of cancer patients was proportional to the extent of weight loss [70], and was reduced in patients responding to chemotherapy [71]. In general, LMF is absent or present in small amounts in tumours that do not induce cachexia [72], and is absent from normal serum, even during starvation [73].

Protein Mobilising Factors

There is evidence for the existence of protein mobilising factors (PMFs) in the sera of animals [74] and humans [75] with cancer cachexia, but not in the sera of healthy controls. In addition, PMFs could not be detected in the urine of healthy individuals, in the urine of patients who developed weight loss due to reasons other than cancer, or in the urine of cancer patients with no cachexia. Injecting PMF into non-tumour bearing-mice resulted in rapid weight loss with no change in food and water intake [5], while an analysis of body composition showed selective depletion of lean body mass [5].

Role of Ghrelin in Cachexia

Many aspects of appetite regulation that involve peripheral signalling to hypothalamic pathways remain poorly understood. Growth hormone (GH) secretion from the anterior pituitary is regulated by GH-releasing hormone (GHRH), which stimulates the release of GH as well as its inhibitor somatostatin [76]. GH secretagogues are synthetic compounds able to stimulate secretion of the hormone [77] but which act through a receptor different from that for GHRH receptor. Instead, ghrelin was discovered to be the natural ligand for that receptor. Ghrelin is mainly secreted by gastric endocrine cells in the fundus into the systemic circulation [78]. Fasting increases, while feeding decreases circulating ghrelin concentrations [78]. These changes are negatively correlated with the serum concentrations of leptin and insulin.

The infusion of ghrelin stimulates eating and produces obesity in rats [79], and a study in humans showed that ghrelin infusion led to short-term increase in hunger [80]. Maintenance of weight reduction after gastric bypass surgery was suggested to be due to markedly low levels of ghrelin [76]. It has also been shown that ghrelin levels are elevated in cachectic patients with chronic heart failure or anorexia nervosa [78]. Several studies are currently underway to explore the effects of ghrelin and its agonists on cachexia.

Role of the Central Melanocortin System in Cachexia

The melanocortin system can be defined as the hypothalamic and brain-stem neurons expressing pro-opiomelanocortin (POMC), hypothalamic neurons expressing neuropeptide Y (NPY) and melanocortin antagonist agouti-related protein (AgRP), and the neurons downstream of these systems [81]. POMC is a propeptide precursor synthesised in neurons in the hypothalamic arcuate nucleus. There are two central melanocortin receptors, melanocortin-3 receptor (MC3-R) and

melanocortin-4 receptor (MC4-R) [81]. Evidence that melanocortin plays a role in energy homeostasis in humans stems from the presence of obesity syndromes involving defects in two different steps in the melanocortin pathway [81].

Some studies have led to the assumption that melanocortin neurons mediate the anorexic effects of elevated leptin, while others have shown that the melanocortin system exerts its effects independent of leptin [81]. POMC neurons mediate the inhibition of food intake and energy storage through the production of α-melanocyte-stimulating hormone (MSH) from a POMC precursor [81]. Central administration of MC4-R agonist can lead to inhibition of food intake, increasing energy expenditure, lower serum insulin, and reduced body weight [81], whereas inhibition of the melanocortin system with an antagonist, or deletion of MC4-R, leads to hyperphagia and obesity [82, 83].

Diagnosis and Screening for Cachexia

The rate of detection of cachexia is low among physicians. Even after diagnosis was made, appropriate intervention was instituted in only one-third of the patients, according to one study [84]. The low rates of detection and intervention are most often due to the inability to make the diagnosis [85]; thus, there is a need for improved screening for cachexia [85]. The Mini Nutritional Assessment (MNA) is a well-validated tool that was specifically designed for use with community-dwelling elderly [85]. The positive predictive value of the MNA for detecting cachexia is 97%, while its sensitivity is 96% and its specificity is 98%. The MNA incorporates several domains, including functional status, lifestyle, diet, self-evaluation of health, and anthropometric indices [86], and does not require laboratory tests. Another screening tool for undernutrition is the DETERMINE questionnaire, which was designed for community-dwelling elderly, and is self-administered [87]; however, it still needs to be validated. The SCREEN questionnaire has been validated and successfully used in Canada [88]. The mini-CNAQ was developed to pick up early changes in appetite in older persons [89]. The SCALES assessment is a useful, sensitive screening tool (Table 4) that is simple to use and easy to administer [88]. The inclusion of data on cholesterol and albumin levels make SCALES sensitive enough to allow the physician to accurately diagnose cachexia. Table 5 provides an overview of the different laboratory tests for deter-

Table 4. Examples of geriatric nutritional assessment tools

A. Mini-CNAQ (pronounced 'snack')
(Council of Nutrition Appetite Questionnaire)

1. My appetite is
   - A. Very poor
   - B. Poor
   - C. Average
   - D. Good
   - E. Very good
2. When I eat
   - A. I feel full after eating only a few mouthfuls
   - B. I feel full after eating about a third of a meal
   - C. I feel full after eating over half a meal
   - D. I feel full after eating most of the meal
   - E. I hardly ever feel full
3. Food tastes
   - A. Very bad
   - B. Bad
   - C. Average
   - D. Good
   - E. Very good
4. Normally I eat
   - A. Less than one meal a day
   - B. One meal a day
   - C. Two meals a day
   - D. Three meals a day
   - E. More than 3 meals a day

Instructions: Complete the questionnaire by circling the correct answers and then tally the results based upon the following numerical scale: A = 1, B = 2, C = 3, D = 4, E = 5
Scoring: If the mini-CNAQ is less than 14, there is a significant risk of weight loss

B. SCALES

Sadness
Cholesterol
Albumin
Loss of weight
Eating problems
Shopping problems

Table 5. Laboratory tests for determining cachexia in older persons

Test	Comment
Weight loss	Best test; < 5% in 3 months or 10% in 6 months
Body mass index (BMI)	< 21 is highly suggestive
Midarm muscle or calf	Good indicators of loss of muscle mass muscle circumference
Albumin/prealbumin	Very low levels suggest cachexia or nephrotic syndrome or liver disease
Cholesterol	Low levels in cachexia
Haemoglobin	Anaemia usually coexists with cachexia
CD4 T-cells	Decreased in severe cachexia and starvation
C-reactive protein	Elevated in cachexia
Interleukin-2 receptors	Elevated in cachexia
Uric acid	Elevated in cachexia

mining cachexia in older persons.

In addition to using a screening tool for malnutrition, it is also important to look for risk factors. Identifying risk factors of malnutrition helps the physician to develop strategies that allow the patient to be well-nourished at all times. The risk factors of malnutrition can be grouped by the mnemonic 'MEALS ON WHEELS' (Table 6).

In the clinical setting, weight measurement and calculation of body mass index are the most widely used indices for nutritional assessment. The use of biochemical markers to assess and treat nutritional risk is discouraged because they have poor predictive value [89, 90]. The most cost-effective parameter of proven clinical usefulness in monitoring nutritional status is body weight measurement [91]. The hallmark of a well-designed nutritional surveillance program is the ability to detect impending nutritional compromise long before laboratory indices become abnormal.

Table 6. The risk factors of malnutrition grouped by the mnemonic 'MEALS ON WHEELS'

Medications (polypharmacy, herbal preparations)
Emotional risk factors (dysphoria, depression, psychosis)
Appetite disorders (anorexia tardive, abnormal eating attitudes)
Late-life paranoia (social isolation)
Swallowing disorders
Oral factors (tooth loss, periodontal infections, gingivitis, poorly fitting dentures)
No money (poverty)
Wandering (dementia)
Hyperactivity/hypermetabolism (tremors, movement disorders, thyrotoxicosis)
Enteral problems (chronic diarrhoea, malabsorption syndromes)
Eating problems (altered food preferences, decreased taste and flavor perception)
Low-nutrient diets (low-salt, low-cholesterol, antidiabetic diets)
Shopping and food preparation problems (impaired mobility, unsafe environment, inadequate transportation)

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