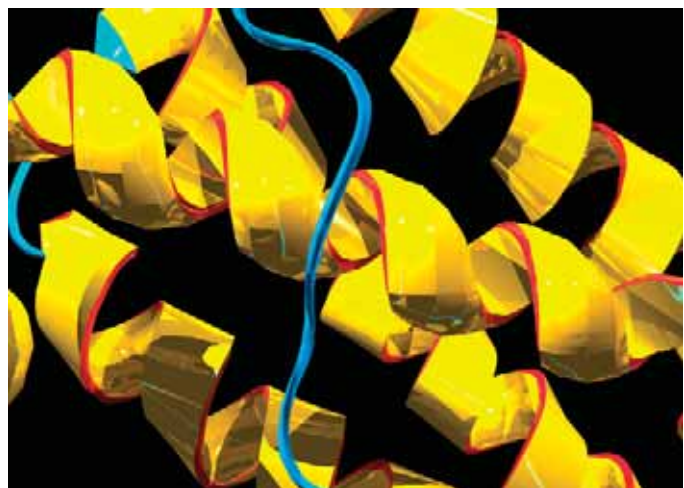


Anorexia-cachexia

— the condition and its causes

By Pam Mason, PhD, MRPharmS

Anorexia-cachexia is a wasting condition commonly seen in patients with cancer or AIDS. The first part of this special feature describes the biochemical abnormalities thought to cause this condition, and the techniques used to detect it



Computer model of part of a leptin molecule: Leptin secretion is increased in cachexia

Anorexia-cachexia is a progressive wasting condition that commonly affects people in the advanced stages of diseases such as cancer and acquired immune deficiency syndrome (AIDS). It is described by loss of appetite (anorexia) and loss of weight (cachexia). The word “anorexia” comes from the Greek word *orexis* (meaning “appetite”), literally translating to “without appetite”. The word “cachexia” is derived from the Greek words *kakos* (meaning “bad”) and *hexis* (meaning “condition”).¹

Anorexia-cachexia is a complex, life-threatening condition in which there is early satiety, loss of appetite, chronic nausea, involuntary weight loss, tissue wasting, loss of muscle, severe fatigue, weakness, poor physical performance and poor immune function.¹ It is a significant cause of psychological distress to patients and to their families, friends and carers.

Anorexia-cachexia occurs in several chronic, end-stage conditions including cancer, AIDS, chronic obstructive pulmonary disease, heart, renal and hepatic failure, inflammatory bowel disease (eg, Crohn’s disease), cystic fibrosis, rheumatoid arthritis and bacterial and parasitic diseases.²

This condition affects nearly half of cancer patients. However, severe cachexia develops in most patients with advanced cancer or advanced AIDS. At the time of diagnosis, about 80 per cent of patients with upper gastrointestinal cancers and 60 per cent of patients with lung cancer have substantial weight loss.³ In pancreatic cancer, 85 per cent of patients develop cachexia.⁴ In general, patients with haematological malignancies or breast cancer do not tend to have substantial weight loss, but most other solid tumours are associated with a high frequency of cachexia.

Cachexia is more common in children and older people and becomes more severe as disease progresses. Overall, more than 80 per cent of patients with cancer or AIDS develop cachexia before they die. In more than 20 per cent of patients, cachexia is the main cause of death.³

Causes

The exact causes of anorexia-cachexia are not clearly understood. However, it would appear to be caused by a combination of reduced energy intake and increased energy expenditure.

Reduced energy intake Reduced intake of calories is seen almost universally in patients with cachexia. The causes of reduced energy intake are listed in Panel 1

(p251). Although reduction in energy intake is common in patients with cachexia for these reasons, in many patients, there seems to be no obvious clinical cause. In healthy people, weight loss normally stimulates food intake. In patients with cachexia, food intake is inadequate to prevent weight loss. The persistence of anorexia in cachexic patients suggests a failure in this adaptive feeding response.

Increased energy expenditure Attempts to increase calorie intake in cachexic patients using methods such as dietary counselling, enteral and parenteral nutrition and appetite stimulants (eg, cyproheptadine, megestrol acetate — see p257 and 263) do not effectively reverse the process of cachexia.¹ In any case, reduced energy intake is not solely responsible for the profound weight loss and body composition changes seen in cachexia. Patients can develop cachexia even in the absence of anorexia. This suggests that increased energy expenditure contributes to the wasting observed (see Panel 2, p251).

Complications Cachexia is a major cause of morbidity and mortality. It increases susceptibility to secondary conditions and reduces survival.³ Cachexia impairs the response to treatment such as chemotherapy, radiotherapy and surgery, and also increases the complications of such treatments.

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Panel 1: Causes of reduced energy intake

- **Dysphagia** Head and neck pain in upper gastrointestinal cancers can inhibit the ability to swallow
- **Disease treatment** In patients receiving chemotherapy or radiation therapy, nausea, vomiting, taste changes and stomatitis can all contribute to reduced calorie intake and malabsorption
- **Gastrointestinal obstruction** Gastrointestinal obstruction may be due to cancer or intestinal surgery
- **Pain** Pain is common in severe disease and can inhibit the desire to eat
- **Psychological distress** Anxiety and depression are common in patients with cancer and other severe diseases as a result of uncertainties about the disease, its diagnosis, treatment and prognosis — this too can reduce food intake
- **Hypercalcaemia** Cancer-associated hypercalcaemia is a fairly common medical emergency and leads to nausea, vomiting and loss of appetite

— Biochemical abnormalities

A number of hormones, neuropeptides and biochemical signals are involved in feeding and tissue metabolism. Anorexia-cachexia leads to disruption in several of these mediators. This disruption is both caused by, and the result of, the acute phase response, which is characteristic of anorexia-cachexia. Key biochemical abnormalities include increased cytokine production, disruption of neuropeptide Y regulation and abnormalities in carbohydrate, fat and protein metabolism.

Increased cytokine production Cytokines have been proposed as key mediators of anorexia-cachexia.⁷ Cytokines are proteins released by macrophages, monocytes and lymphocytes in response to trauma, malignancy and sepsis. Several cytokines have been proposed as mediators of the cachexic process. These include tumour necrosis factor- α (TNF- α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interferon- γ . High serum concentrations of TNF- α , IL-1 and IL-6 have been found in some cancer patients. Levels of these cytokines seem to correlate with the progression of the tumours.⁷

Chronic administration of these cytokines in animals is associated with a reduction in food intake and the features of anorexia-cachexia. These cytokines are thought to produce long-term reduction in feeding by stimulating the secretion of the hormone leptin by the adipose tissue as well as increasing its expression.

Leptin plays an important role in body weight regulation. This includes triggering the adaptive response to starvation. Starvation and the resulting weight loss cause leptin levels to fall. Low leptin levels in the brain increase the activity of the hypothalamus to stimulate feeding and reduce energy expenditure. Low leptin also decreases the signals that suppress appetite and increase energy expenditure. These mechanisms may play an important role in the recovery of lost body weight in cases of starvation.

In cachexia, however, the increase in leptin secretion caused by increased cytokine concentrations may prevent these compensatory mechanisms that normally occur in the face of weight loss. Cytokines also influence other mediators linked with the development of anorexia-cachexia. For example, pro-inflammatory cytokines induce the release of corticotrophin-releasing factor, which is a potent inhibitor of feeding.⁷

Disruption of neuropeptide Y regulation

Neuropeptide Y (NPY) is a 36-amino acid peptide found in the brain, including the hypothalamus. It is the most potent of the feeding stimulatory peptides and is part of a biochemical network of other hormones and peptides. NPY may stimulate feeding on its own or through interaction with its network of associated mediators.

However, in anorexia-cachexia, NPY-induced feeding appears to fail. Increased leptin levels, seen in cachexia and caused by increased cytokine production, can block NPY and induce satiety. Cytokines can therefore block NPY, while NPY can block cytokine-induced anorexia-cachexia. This antagonistic interaction between cytokines and NPY is important in the development of anorexia-cachexia.⁸ Dysfunction in NPY-induced feeding has been demonstrated in rats with malignancies.

Abnormalities in carbohydrate, fat and protein metabolism Anorexia-cachexia is associated with changes in nutrient metabolism,⁶⁻⁹ as described in Panel 3 (p252).

— Detection

There are no specific diagnostic criteria for cachexia but the basic diagnosis is usually straightforward. The patient's clinical history, the presence of substantial weight loss and physical examination together give a clear picture of the condition. Measurements made may include the following:

Body weight Body weight can be compared with reference ranges and is a crude measure of nutritional status. However, change in body weight is an important indicator of nutritional status. Unless a person is attempting to lose weight, weight fluctuation over time is usually narrow, tending to vary by no more than 5 per cent over a six-month period.¹² Weight loss exceeding 5 per cent is likely to be of clinical significance, particularly if the weight loss is rapid or if undernutrition is clearly present.

Panel 2: Energy expenditure

Total energy expenditure is made up of voluntary energy expenditure, resting energy expenditure and thermogenesis induced by food intake and digestion.

Voluntary energy expenditure Voluntary energy expenditure is likely to be reduced in cachexic illnesses, which may manifest as apathy, weakness and depression.

Resting energy expenditure (REE) There are conflicting reports about REE in cachexic diseases.⁵ Increases in REE have been reported in patients with lung and pancreatic cancer, but not in patients with gastric and colorectal cancer, even where these patients have weight loss. Given that overall energy expenditure usually falls with reduced food intake and weight loss, lack of increase in REE may represent an abnormal metabolic situation. Regulation of food intake in relation to energy expenditure may therefore be imperfect in cachexic patients.

Diet-induced thermogenesis In humans, thermogenesis occurs mainly in skeletal muscle. Brown adipose tissue (BAT) which is an important site of thermogenesis in rats, is of less importance in humans because we have less of it. However, there is evidence that BAT increases in humans with cachexia, so both skeletal muscle and BAT may play a role in thermogenesis in these patients. Thermogenesis is activated by the sympathetic nervous system through induction of the mitochondrial uncoupling proteins.⁶ Due to the action of these proteins, energy from oxidation of food is not used in the usual way for synthesis of adenosine triphosphate (ATP) but rather released as heat. This may contribute to the reduced energy efficiency and wasting found in cachexic patients.

Panel 3: Changes in nutrient metabolism

Carbohydrate metabolism An increase in hepatic glucose production occurs to meet the metabolic demands of the cachexic patient. In cancer cachexia, the tumour uses glucose as the primary source of energy. It then produces large amounts of lactate, which is converted back into glucose in the liver, a process known as the Cori cycle.¹ This process (glucose to lactate to glucose) is energy consuming and contributes to the development of cachexia. In addition to lactate, glucose synthesis from alanine and glycerol is increased. Breakdown of protein and fat therefore occurs at increased rates to maintain the high level of glucose synthesis. In addition, insulin secretion may be defective, normal or increased, but insulin resistance in the adipose tissue, skeletal muscle and liver is common, leading to reduced tissue uptake of glucose and glucose intolerance.

Fat metabolism The energy demand of the cachexic patient leads to accelerated loss of adipose tissue, which contributes to most of the weight loss in cachexia. Increased fat breakdown results in increased levels of glycerol and fatty acids in the blood. Both are used as substrates for glucose production; glycerol is directed to the liver and fatty acids to other tissues. The increased fat mobilisation is thought to be due to lipid-mobilising factor, produced in cancer cachexia by the tumour.¹⁰ Another suggested mechanism for the accelerated loss of fat tissue is decreased activity of lipoprotein lipase (LPL), the enzyme responsible for triglyceride clearance from the plasma.⁹ This would prevent adipose tissue from extracting fatty acids from plasma lipoproteins for storage, resulting in a net flux of lipid into the circulation and causing hyperlipidaemia (hypercholesterolaemia and hypertriglyceridaemia). Inhibition of LPL may be caused by cytokines.

Protein metabolism Patients with cachexia experience loss of lean body mass and muscle wasting due to decreased protein synthesis and increased protein breakdown. This reduces physical strength, contributes to poor immune function and shortens survival time. Muscle wasting and weight loss have been shown to correlate with serum levels of proteolysis-inducing factor (PIF). PIF is capable of inducing protein breakdown as well as inhibiting protein synthesis. It appears to activate various proteolytic pathways mediated by ubiquitin that induce skeletal muscle breakdown.¹¹

Rapid weight loss over a few days reflects changes in fluid balance rather than body tissue. Sequential body weight measurements taken at weekly intervals using hospital admission weight are a simple and useful way of monitoring nutritional status unless significant fluid retention is present (eg, oedema or ascites).

Skinfold thickness¹² Measurement of skinfold thickness at specific body sites can be used to estimate body fat. Skinfold thickness is measured by pinching a fold of skin with subcutaneous fat between a pair of skinfold callipers. The most accurate estimates of body fat require skinfold measurements at a number of sites (eg, the triceps, biceps, subscapular and iliac crest). In clinical practice and especially in bed-bound patients, triceps skinfold thickness alone is most commonly used as an indicator of body fat stores. In conjunction with the mid-arm circumference, it can be a useful way of estimating body composition in patients with ascites or peripheral oedema or who cannot be weighed. However, loss of body weight results in non-proportional changes in muscle and fat stores at different sites, making it difficult to compare measurements with reference values from normal controls.

Body composition¹² Measurement of body weight does not discriminate between lean

tissue and fat mass. However, body composition can be measured by bioelectrical impedance analysis (BIA). BIA is based on the principle that lean tissue, with its high water and electrolyte content, is highly conducive to electrical current, while fat tissue is resistant. By measuring the change in voltage when a small current is passed through electrodes placed on specific parts of the body, a measurement of total body water (TBW) can be made. Fat free

mass (FFM) is estimated from TBW by assuming that it comprises 73 per cent of the body's water content. Body fat can be determined by subtracting the estimate of FFM from the total body weight. Although not used routinely, BIA may become more important in the future than measurement of body weight.

Laboratory tests Serum proteins such as albumin and transferrin and urinary metabolites, such as creatinine have traditionally been used as markers of nutritional depletion. However, many of these are of limited value in anorexia-cachexia due to the complex and chronic nature of the condition.¹⁴

— Management

Options for management of cachexia include increasing nutritional intake, and prescribing drugs to inhibit muscle and fat wasting (see p257). Educational, psychological (see Panel 4) and behavioural therapies are also important. Co-morbidities such as anxiety, dysphagia, nausea, dehydration, constipation and oral or systemic infections should also be assessed and managed.

— Nutrition

Causes of reduced food intake and poor appetite (such as nausea and vomiting resulting from treatment, oral mucositis and gastrointestinal obstruction) should be identified and if possible managed with palliative interventions.

Improving appetite and food intake is not associated with improved survival, but may improve the patient's and family's quality of life and sense of well being. Improving food intake can be attempted by:

- Offering the patient favourite foods and nutritional supplements (if the patient enjoys them)

Panel 4: Psychological interventions

Complementary therapies such as hypnosis, relaxation and short-term group psychotherapy may be of benefit, but the type of patient most likely to benefit has not been determined.¹⁴ Counselling can often be effective and pharmacists, like any other member of the health care team, can provide this. Counselling should include:

- Encouraging patient and family interaction which can reduce psychological distress in both parties
- Educating and supporting the family and caregivers as well as the patient
- Helping the family and carers to distinguish between the normal progression of the disease (over which they have no control) and things they can do to help the patient feel better
- Exploring the emotional components and the meaning of the patient not eating, losing weight or not having energy
- Assessing how much the patient is bothered by the symptoms, while realising that the family may be more distressed than the patient
- Assessing the quality of life of both patient and family

- Eliminating dietary restrictions
- Reducing portion sizes and making food look appetising
- Avoiding food smells that the patient dislikes
- Encouraging an alcoholic drink (if the patient enjoys this) as alcohol has appetite stimulating properties

Because cachexia is often thought to be a condition of energy deficit, enteral and parenteral nutrition support has been tried. Unfortunately, intensive nutrition does not increase lean tissue mass, especially skeletal muscle mass. No significant improvement in patient survival or tumour shrinkage has been demonstrated,¹³ and complications associated with surgery, radiotherapy and chemotherapy are not significantly reduced. Indeed, an increase in infections and mechanical complications has been reported.¹⁴

However, intensive nutrition is appropriate in certain clinical situations such as in patients recovering from surgery or waiting for chemotherapy. Parenteral nutrition may ease administration of complete doses of chemotherapy and radiotherapy in oesophageal cancer¹⁵ and may be of benefit where food intake is reduced because of gastrointestinal obstruction. If the gut can be used for nutritional support, enteral nutrition has the advantages of maintaining the gut mucosal barrier, maintaining immune function, safety and low cost.

Supplementation with omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) has been shown to interfere with mechanisms associated with cachexia (eg, reducing the production of inflammatory cytokines). As a consequence, EPA has been used to decrease weight loss, promote weight gain and improve survival times in patients with cancer-cachexia. Studies have shown trends in favour of EPA, although a Cochrane review concluded that there are insufficient data to establish whether EPA is better than placebo (see p258).¹⁶

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