# Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia: overlap of clinical features

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**Purpose of review**
Malnutrition, fatigue, frailty, vulnerability, sarcopenia and cachexia all phenotypically present with the same features because they are subject to the operation of similar mechanistic factors. However, the conditions referred to above differ by which mechanism dominates the cause of the clinical condition. This review discusses the overlap and differences, which distinguish as well as unite these different conditions and allow a rationale for treatment.

**Recent findings**
In the continuum of malnutrition, cachexia, sarcopenia and frailty the recent activities focus on two areas. The first is a better understanding of the mechanisms of cachexia and sarcopenia and frailty. In particular, the differential effects of cytokines on muscle and on the hypothalamic system. The effects of inactivity promoting the loss of body mass in cachexia and sarcopenia as well as the positive effects of exercise. The second is the development of a synthesis of available literature to develop consensus documents about the definition, causes, diagnosis and treatment of cachexia, sarcopenia and frailty.

**Summary**
Loss of body tissues resulting in wasting is a common phenotype for several different conditions which can be caused by a combination of reduced food intake, excessive requirements, altered metabolism, sepsis, trauma, ageing and inactivity. They have been referred to loosely as malnutrition but in not all will respond to simply providing nutrients. In this review the common features and the differences as they relate to cause and response to treatment are discussed.

**Keywords**
ageing, cachexia, cancer, malnutrition, sarcopenia, sepsis, trauma

## INTRODUCTION

Loss of weight caused by loss of the body tissues is associated with a number of conditions which range from deliberate desire to lose body fat [1▪▪] to disease-induced inexorable and unwanted weight loss progressing to extreme weakness and death. The latter is called cachexia but despite a myriad of expert opinions and even a recent consensus conference, the understanding remains elusive as shown by the rather broad definition proposed [2] 'cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass. 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 [3▪]. Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity'. Unfortunately, the mechanism as discussed below overlaps between 'cachexia' and many of the conditions from which it is supposed to be distinguished [4]. Another condition of tissue loss is age-related muscle loss that has been referred to as 'sarcopenia' [5▪▪,6▪], a term coined by Irwin Rosenberg [7,8]. It is a predominant loss of muscle without loss of fat much like that in cachexia.

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**Curr Opin Clin Nutr Metab Care** 2012, 15:213–219
DOI:10.1097/MCO.0b013e328352694f

## KEY POINTS

- Many conditions look phenotypically like the starved person but do not respond to feeding.
- The term malnutrition should be applied only to conditions, which dramatically respond to feeding.
- Nutrient support may be an adjuvant to conditions not strictly due to a simple lack of food and/or increased requirements.
- Exercise is an important treatment modality for a number of conditions resulting in body wasting.

In this section the features and potential causes of weight loss and overlap of different conditions leading to the same phenotypic changes will be discussed. Instead of refining definitions a mechanistic approach may create better insight and help design appropriate treatment.

## PHENOTYPICALLY UNIFIED ETIOLOGICALLY DIFFERENT

The unifiying feature of all the above conditions is a loss to a greater or lesser extent of body muscle and fat. However, the lumping together of these terms is a confusion in concept. Malnutrition implies a mechanism namely imbalance of protein-energy status. Strictly malnutrition may not imply any wasting, for example zinc deficiency and acrodermatitis. In contrast the term cachexia is derived from the Greek words kakos, which means bad and hexis, which means condition and applies to the appearance of a very sick wasted person. When we say a person is cachectic we are defining a phenotypic state. However, the same phenotypic state can be seen after prolonged starvation, cancer, sepsis, ageing resulting from different causes and responding in different ways to treatment. We therefore need to examine these terms carefully and think in terms of disease mechanisms rather than terminology.

## BASIC CAUSES OF TISSUE LOSS

There are five basic mechanisms discussed below which operate to a variable extent as being the causes of the clinical condition we refer to as malnutrition, cachexia, sarcopenia and frailty.

### Energy intake insufficient to meet energy requirements

Food eaten is metabolized to provide energy for organ function and muscle activity. If intake is insufficient to meet needs, body tissues are catabolized to provide energy. The deficit may be caused by both reduced intake and increased requirements. The latter is called hypermetabolism. Body fat is the main store of energy and is initially used so that body fat loss dominates the wasting seen with this situation.

### Increased cytokine activity

Increased levels of tumour necrosis factor (TNF)-$\alpha$, interferon-$\gamma$ (INF-$\gamma$), interleukin (IL)-6 are associated with increased thermogenesis and fever, increased muscle catabolism and reduced muscle protein synthesis.

### Reduced muscle loading

Muscles waste away and weaken if not subject to loading and stress. Weightlessness, bed rest, and inactivity all reduce muscle mass and strength [9▪▪]. In addition amino acids fail to stimulate protein synthesis without the stimulus of exercise [10].

### Hormonal action

Insulin is required for anabolism of muscle and fat. Insulin deficiency as seen in type I diabetes is associated with marked loss of body muscle and fat. Corticosteroids increase lean tissue catabolism resulting in thinning of skin, muscle and bone loss. Testosterone levels aid muscle development. Catacholamines and sympathetic overactivity increase metabolic rate and result in tissue loss.

### Neuromuscular atrophy

Loss of neural end plates cause muscle fiber loss and remodeling to replace high tension type II fibers by type I fibers. Muscle inflammation and diseases or conditions affecting peripheral nerves cause muscle atrophy.

## CLINICAL SYNDROMES OF BODY TISSUES LOSS

The above mechanisms operate to a variable extent in concert with some dominating and others assisting in the well known clinical presentations given below. Therefore, it is not surprising that these conditions overlap in their presentation and often occur together, making it difficult to define the exact clinical syndrome in any one patient.

## Protein-energy imbalance malnutrition

In nature protein and energy (collective term for carbohydrate and fat) nutrients exist together to a greater or lesser extent, and therefore an imbalance between intake and needs occur collectively for these nutrients (Fig. 1a). In the early stages of malnutrition muscle is protected as energy and protein requirements are met by use (therefore loss) of liver glycogen and body fat associated with the mobilization of labile protein stores from the viscera. The initial net result of a pure imbalance of protein-energy nutrition is progressive loss of liver glycogen and labile protein followed by progressive loss of body fat which reduces muscle catabolism.

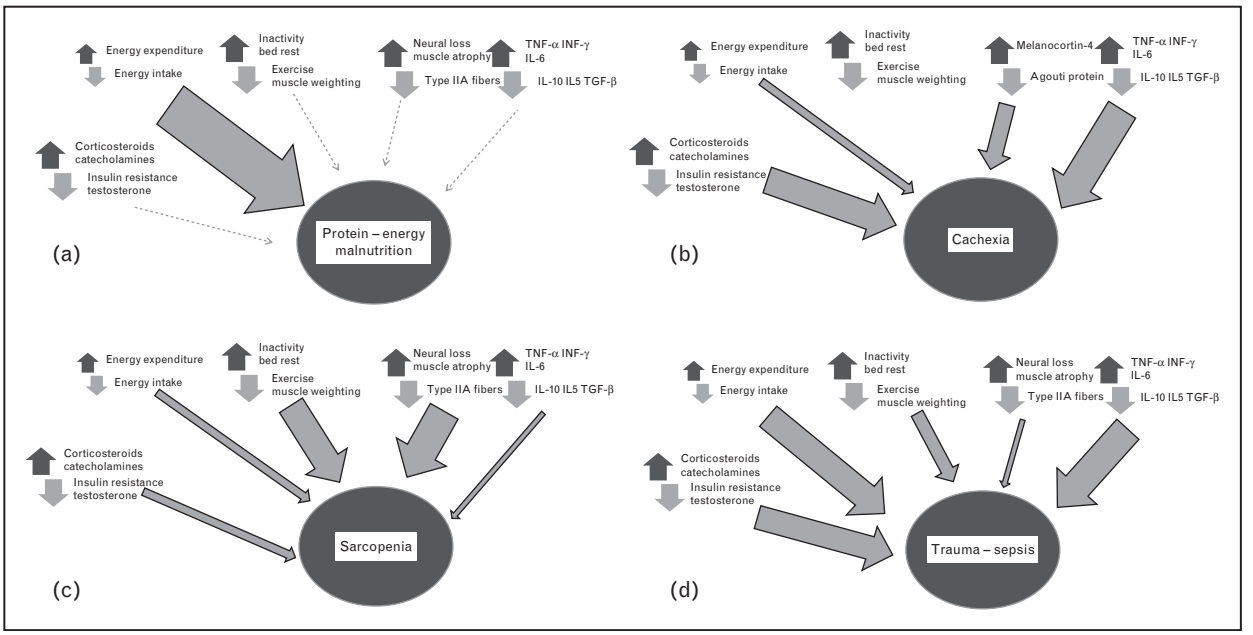


**FIGURE 1.** (a) The factors, which influence body composition in malnutrition. The upward arrows indicate that the factor indicated beside the arrow increased and the downward arrow indicates which factor decreased. In this context corticosteroids–catecholamines represent catabolic hormones and testosterone and insulin resistance increasing insulin levels ate anabolic factors. In addition, increased neural and muscular atrophy and decreased type IIA fibers contribute to wasting. The degree to which these factors contribute to malnutrition is reflected in the width of the arrow pointing to the central oval. In pure protein-energy malnutrition the intake and requirements of nutrients dominate the occurrence of malnutrition. Other factors also have a lesser role as indicated. (b) The factors, which influence body composition in cachexia. The upward arrows indicate that the factor indicated beside the arrow increased and the downward arrow indicates which factor decreased. In this context corticosteroids–catecholamines represent catabolic hormones and testosterone and insulin resistance increasing insulin levels ate anabolic factors. The degree to which these factors contribute to cachexia is reflected in the width of the arrow pointing to the central oval. In the genesis of cachexia the dominant factors are cytokines, hormones and the central effect on the hypothalamus increasing melanocortin-4 and reducing Agouti protein. Other factors also have a lesser role as indicated. (c) The factors, which influence body composition in sarcopenia. The upward arrows indicate that the factor indicated beside the arrow increased and the downward arrow indicates which factor decreased. In this context corticosteroids–catecholamines represent catabolic hormones and testosterone and insulin resistance increasing insulin levels ate anabolic factors. In addition, increased neural and muscular atrophy and decreased type IIA fibers contribute to wasting. The degree to which these factors contribute to sarcopenia is reflected in the width of the arrow pointing to the central oval. In the genesis of sarcopenia the dominant factors are reduced activity and neural fiber loss with reduction in type IIA fibers. However, anorexia, increased cytokine levels with ageing and hormonal changes also contribute to sarcopenia. (d) The factors which influence body composition in acute illness the upward arrows indicate that the factor indicated beside the arrow increased and the downward arrow indicates which factor decreased. In this context corticosteroids–catecholamines represent catabolic hormones and testosterone and insulin resistance increasing insulin levels ate anabolic factors. In addition, increased neural and muscular atrophy and decreased type IIA fibers contribute to wasting. The degree to which these factors contribute to wasting in trauma–sepsis is reflected in the width of the arrow pointing to the central oval. In the genesis of wasting in trauma and sepsis the dominant factors marked increase in energy expenditure with inability to eat due to unconsciousness and artificial ventilation unless nutritional support is given. Increase in catabolic hormones and cytokines are important. Bed rest and immobility are other factors.

However, some muscle loss though minimal, occurs but can be prevented by exercise. In this context exercise has a major protective effect against muscle loss. However, as the imbalance becomes prolonged, body stores of nonprotein energy namely glycogen and fat disappear and survival depends upon consuming body protein. At this point the phenotypic appearance is identical to cachexia. The studies of Irish hunger strikers showed that loss of body protein resulted in death [11]. Hence, from a study of advanced protein-energy imbalance we have a mechanistic lesson for cachexia, namely that severe protein deficiency is likely to be the cause of death.

## Disease-induced wasting and fatigue cachexia

It is clinically a feature of infection-sepsis, cancer, heart failure, arthritis and chronic pulmonary disease (Fig. 1b). A consensus document on cachexia [2] has pointed out that the term 'malnutrition' has often been used to describe cachexia and should be avoided as cachexia 'cannot be successfully treated with nutrition alone'. A major difference between a unique imbalance of protein-energy status and cachexia is the early and profound loss of muscle mass seen with cachexia [2,3▪]. In contrast, muscle loss is a late manifestation of protein-energy imbalance. Cachexia with profound muscle loss may be associated with increased body fat called 'cachectic obesity'. In a recent systematic literature review, the reviewer pointed out that the analysis was clouded by the variety of definitions used to include patients defined as being cachectic. The review showed that while cachexia does not respond to nutritional support there is negative protein energy balance due to both reduced intake and abnormal metabolism leading to progressive functional impairment [12].

The recognition of cachexia is based on the presence of three of the following five criteria [2]:

(1) Weight loss of at least 5% body weight or BMI $<20\,kg/m^2$ in the absence of simple starvation.
(2) Decreased muscle strength.
(3) Fatigue.
(4) Anorexia.
(5) Low fat-free mass index ($<7.26\,kg/m^2$ in men and $<5.45\,kg/m^2$ in women).
(6) Abnormal biochemistry increased corticotrophin releasing factor (CRP), reduced albumin, anemia.

In addition reduced muscle function disproportionate to loss of muscle mass occurs and causes profound weakness. In contrast pure imbalance of protein-energy does not cause early fatigue. For example, anorexic patients are hyperactive and rarely fatigued.

The mechanism of muscle loss in cachexia is related to both a direct action of cytokines and indirect effects through the hypothalamus.

### Direct effect of cytokines

The direct effect of two proinflammatory cytokines TNF-α and INF-γ are to activate nuclear factor-kappa B (NF-κB) from its inhibitory protein resulting in the subsequent activation of the ubiquitin–proteosome pathway resulting in myofibrillar proteolysis and muscle loss [13,14]

### Hypothalamic effects

Inflammation and cancer in the peripheral tissues increase levels of cytokines in the hypothalamus, resulting in the secretion of α-melanocyte stimulating hormone (α-MSH) by the pro-opiomelanocortin (POMC) neurons and inhibition of Agouti-related protein (AgRP) neurons. α-MSH activates melanocortin-4 resulting in increased metabolic rate, anorexia and lethargy. Muscle loss and insulin resistance also occurs as a result of release of CRP increasing the secretion of adrenocorticotrophic hormone and glucocorticoids [15].

## Age related wasting (sarcopenia and frailty)

The term sarcopenia was coined by Irwin Rosenberg [8] to describe age-related muscle loss (Fig. 1c). After the age of 30 years the basal metabolic rate falls at the rate of 3–8% per decade and it is entirely due to involuntary loss of muscle because the metabolic rate corrected for muscle mass does not decline. After the age of 50 years there is a 1–2% loss of muscle per year mainly of type IIa fibers [16]. This change results in loss of strength and endurance.

The definition of sarcopenia is when the appendicular muscle mass divided by height squared is below two standard deviations of the normal young mean ($<7.23\,kg/m^2$ and in women at $<5.67\,kg/m^2$) [17]. This definition shows that sarcopenia increases from 14% in those aged above 65 years but below 70–53% in those above 80 years of age [18]. The loss in muscle may be associated with increased body fat so that despite normal weight there is marked weakness; a condition called sarcopenic obesity. The mechanisms of sarcopenia are not clearly defined [6▪].

There is a reduction in the rate of muscle protein and myofibrillar protein synthesis perhaps due to reduced muscle protein mRNA expression. Type II muscle fiber loss as well as fiber atrophy occur, and

suggests denervation followed by reinervation of muscle.

### Sedentary lifestyle

Individuals who have had an active lifestyle throughout their life have more lean body mass and muscle mass when aged. Controlled clinical trials have shown that exercise will significantly increase muscle strength and to a lesser extent muscle bulk in the aged. The improvement in strength was sufficient to allow stair climbing.

### Activation of cytokines

In aged individuals there are higher levels of cytokines such as TNF-α and IL-6. In addition, obesity and inflammatory conditions such as arthritis contribute to increased cytokine levels.

### Deficiency of hormone

Particularly in men a fall in testosterone levels promotes muscle loss. Resistance to insulin and growth hormone may reduce muscle protein synthesis.

### Frailty

Frailty syndrome is defined as unintentional weight and muscle loss, exhaustion, and decline in grip strength, gait speed and activity [19▪▪]. This is caused by the effect of several different dimensions of lifestyle and include genetics, ageing, poor nutritional choices, for example tea and toast diet, lack of physical activity, smoking and alcohol, lack of mental stimulation and comorbidities, for example diabetes. In this situation the person is vulnerable to become disabled with any additional stress.

### Acute illness

Acute illness results in rapidly developing cachexia (Fig. 1d). Trauma is followed by a phase during which there is uncontrolled hypercatabolism the so-called 'ebb phase', this is followed by a phase during which anabolism increases and there is restoration of lost body components called the 'flow phase'. Sepsis causes marked tissue wasting due to hypercatabolism and reduced muscle anabolism due to a combination of increased cytokine activity and hypothalamic activation causing increased output of corticosteroids [20]. These changes are augmented by an imbalance of reduced intake with increased requirements. However, wasting is not entirely due to a relative or absolute reduction in nutrient intake because increased protein energy feeding maintains or even increases body fat but lean body loss continues to decrease [21]. A combination of increased corticosteroid output, cytokine expression such as TNF-α and IL-6 contribute to muscle loss due to mechanisms similar to those seen with cachexia.

## TREATMENT AND PREVENTION OF WEIGHT LOSS

The distinctions between the different conditions referred to above is important as they cannot be corrected or prevented by the same therapy.

### Role of nutritional support

Anorexia or impediment to food intake is the dominant cause of weight loss and wasting in conditions of pure protein-energy imbalance. Anorexia may also contribute to weight loss in some patients with cachexia and sarcopenia. In acute illness the inability to eat because of severe prostration, unconsciousness contributes to weight loss and wasting. The role of nutritional support in reversing weight loss and wasting depends upon the extent to which reduced intake contributes to the picture of wasting and weight loss. Hence the ability of feeding alone to alter outcome varies from being lifesaving when there is a pure imbalance of protein energy to perhaps even increasing complications in conditions wherein the dominant cause is disease-induced catabolism.

Nutritional support highly effective: the following conditions are entirely due to an imbalance between intake and requirements and respond dramatically to feeding:

(1) Anorexia.
(2) Obstruction of the gastrointestinal tract
    (a) Dysphagia
    (b) Gastroparesis and gastric outlet obstruction
    (c) Intestinal obstruction both mechanical and motor
    (d) Radiation enteropathy.
(3) Maldigestion
    (a) Biliary insufficiency
    (b) Pancreatic insufficiency.
(4) Malabsorption
    (a) Short bowel-intestinal resection
    (b) Intestinal mucosal disease
    (c) Inflammatory bowel disease
    (d) Lymphatic obstruction.

Nutritional support partly effective:

(1) Ageing, sarcopenia and frailty. In these conditions in addition to muscle loss resulting from ageing there is additional effects of reduced appetite and impediments to eating such as lack

of teeth, cognitive disability, lethargy. In a controlled clinical trial nutritional supplement in the aged increased body weight but not muscle mass or strength. The ability to increase intake voluntarily was greatest in those who received nutritional supplement and were subject to strength training exercise [22].

(2) Trauma and ICU patients: trauma without sepsis will respond to nutritional support during the flow phase but muscle loss during the ebb phase is unlikely to change with feeding. In sepsis control of the infection is critical to allowing nutritional support to be effective in restoring body mass but during acute sepsis it is not clear if tissue loss can be altered by nutrition. In theory while increased protein-energy intake should reduce the loss of tissue – so-called hyperalimentation – in practice such increased feeding may be actually harmful in this situation.

(3) Recovering cachexia: the most successful situation is wherein chronic sepsis-related cachexia has been successfully eradicated. Examples are tuberculosis, extensive abdominal sepsis and surgery. The other group are patients with cancer following induction of remission. The treatment of cachexia results in varying degrees of recovery and remission. In addition the treatment modalities like radiation can damage the intestine and cause malabsorption and obstruction. Chemotherapy causes anorexia, intestinal injury and mucositis making food intake difficult. In these conditions while there are no controlled trials nutritional support will prevent or restore wasted tissue.

### Nutritional support ineffective

The term 'ineffective' depends upon the definition of efficacy. If it is simply partial restoration of wasting and even function then with the exception of extreme sepsis or end-stage metastatic cancer, nutritional support will be so effective. However, if efficacy means reduced mortality or complications then under most conditions, which lead to cachexia, nutritional support is ineffective or has not been proven to be effective. The use of aggressive nutritional support in patients at the end of life in palliative care is questionable. However, oral nutrition and fluids to provide comfort should not be denied.

## Role of exercise

Muscle loss and weakness occur in cachexia, sarcopenia and frailty. Muscle weakness reduces the ability to perform daily functions, restricts mobility and increases the risk of falls, which in turn increase or cause disability. Exercise has anabolic effects on muscle and in all these conditions exercise has the potential to reduce the rate of decline or even improve function.

### Sarcopenia and frailty

It has been shown that athletic activity reduces the risk of sarcopenia by building muscle bulk and muscle power. For example, football players at about 65 years of age had the same BMI as controls but had a significantly higher muscle mass and bone density indicating that they are less likely to become sarcopenic or fracture bones [23]. In established sarcopenia a randomized controlled trial of exercise and diet with exercise in 80-year-old patients has shown significant improvement in muscle function and stair climbing.

### Cachexia

Cachexia is also characterized by muscle loss and there is experimental evidence that exercise will override metabolically induced muscle loss. Hence, even in cachexia caused by chronic obstructive pulmonary disease [24] and cancer [25] there may be a role of exercise to slow or prevent muscle loss. However, dyspnoea, weakness and fatigue may limit the ability to do conventional exercise. In order to circumvent these limitations muscle training uses prolonged low loads [26] or use of electrical stimulation [27] achieves improved muscle mass and function.

## Patient with overlapping clinical features

Although there are clearly defined conditions mentioned above a case history will illustrate that in real life these conditions overlap and each patient has to be evaluated as an individual.

A 70-year-old sedentary man has noted increasing difficulty in climbing stairs and getting up from the sitting position. He has noted that his arms and legs are getting thinner. He then falls and has a hip fracture. Postoperatively he develops pneumonia and loses weight in hospital. On recovery from the pneumonia he is anorexic and is unable to stand out of bed. This man has wasting due to a combination of sarcopenia, acutely developing cachexia due to trauma and sepsis and protein-energy imbalance on recovery impeded by anorexia. He needs treatment for pneumonia, hip surgery and supportive nutrition. Once he has overcome the acute phase and sepsis he will require nutritional support/dietetic advice and progressive resistive or strength training exercise.

## CONCLUSION

The different mechanisms of tissue loss occur in variable combinations to create well recognized dominant syndromes of protein-energy malnutrition, cachexia, sarcopenia-frailty and trauma-sepsis (Fig. 1) but in individual patients they operate in various combinations blurring the lines between the different clinical syndromes. Examples of overlap are as follows:

(1) A starving patient is one with protein-energy malnutrition but malnutrition can promote pneumonia which than adds acute sepsis. Starvation and weakness causes inactivity and sarcopenia.
(2) Cachexia in cancer is associated with anorexia and protein-energy malnutrition. The patient successfully treated with surgery radiation and chemotherapy changes with weight loss due to cachexia to protein-energy malnutrition due to radiation enteropathy.

These examples make it necessary to analyze each patient individually and longitudinally to determine the appropriate timing and necessity for nutritional support, exercise or disease treatment to successfully restore body composition, overcome weakness and promote health.

### Acknowledgements

*None*.

### Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 315–316).

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