Cachexia and Sarcopenia: Emerging Syndromes of Importance in Dogs and Cats

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Cachexia is the loss of lean body mass (LBM) that affects a large proportion of dogs and cats with congestive heart failure (CHF), chronic kidney disease (CKD), cancer, and a variety of other chronic diseases. Sarcopenia, the loss of LBM that occurs with aging, is a related syndrome, although sarcopenia occurs in the absence of disease. As many of the diseases associated with muscle loss are more common in aging, cachexia and sarcopenia often are concurrent problems. Both cachexia and sarcopenia have important clinical implications because they are associated with increased morbidity and mortality. The pathophysiology of these 2 syndromes is complex and multifactorial, but recent studies have provided new information that has helped to clarify mechanisms and identify potential new targets for treatment. Newly identified mechanisms and pathways that mediate cachexia appear to act by increasing energy requirements, decreasing energy intake, impairing nutrient absorption, and causing metabolic alterations. Whereas cachexia and sarcopenia are important areas of research for drug development in people, they are only beginning to be recognized in veterinary medicine. Greater awareness and earlier diagnosis will help provide practical approaches to managing body weight and lean tissue in dogs and cats, as well as more directed targets for treatment.

Key words: Inflammation; Lean body mass; Muscle condition score; Nutrition.

In both people and companion animals, cachexia and sarcopenia are 2 important syndromes that occur in a variety of chronic diseases and aging, respectively. Although cachexia has been recognized in people for over 2,000 years, only recently has it become acknowledged as a common and detrimental finding that is associated with increased morbidity and mortality, and with this observation has come rapidly expanding interest and research. Today there is a society (Society on Sarcopenia, Cachexia, and Wasting Disorders) and a journal (Journal of Cachexia, Sarcopenia and Muscle) devoted to the study of these 2 disorders. As a result, concerted efforts are being made to combat these syndromes in people and to improve outcome for the wide variety of diseases with which they are associated.

Both of these syndromes are becoming increasingly important in human and veterinary medicine because of their high prevalence and adverse clinical effects, and a better understanding of the mechanisms underlying these syndromes is critical for optimal patient care, whether human or veterinary. This newfound interest is spurring the development of new drugs, diets, and other treatments to combat cachexia and sarcopenia in people. Our veterinary patients will benefit from this research, but these are important areas to specifically study in dogs and cats during aging and in chronic disease. Therefore, the purpose of this review is to raise awareness of these syndromes and their adverse effects in dogs and cats, as well as to discuss current and future treatments.

Abbreviations:

AAFCO Association of American Feed Control Officials
ACE angiotensin converting enzyme
AIDS acquired immunodeficiency syndrome
ANP atrial natriuretic peptide
BCS body condition score
BMI body mass index
BNP b-type natriuretic peptide
CHF congestive heart failure
CKD chronic kidney disease
COPD chronic obstructive pulmonary disease
CT computed tomography
DCM dilated cardiomyopathy
DEXA dual-energy x-ray absorptiometry
DHA docosahexaenoic acid
EPA eicosapentaenoic acid
IGF-1 insulin-like growth factor-1
IL-1 interleukin-1β
IL-6 interleukin-6
LBM lean body mass
MCS muscle condition score
NF-κB nuclear factor-κB
SARM selective androgen receptor modulators
TNF tumor necrosis factor α

Cachexia

Cachexia, a loss of lean body mass (LBM), has been reported since the time of Hippocrates when people with congestive heart failure (CHF) were described: “the flesh is consumed and becomes water, … the abdomen fills with water, the feet and legs swell, the shoulders, clavicles, chest and thighs melt away … This illness is fatal.”1–3 However, heightened awareness and recognition are increasing its diagnosis in people. More than 5 million people in the United States alone are estimated to have cachexia, which occurs in a variety of chronic diseases, including CHF, cancer, chronic kidney disease (CKD), acquired immunodeficiency disease (AIDS), chronic obstructive pulmonary disease...
(COPD), and rheumatoid arthritis.\(^3\) The syndrome of cachexia also appears to be common in companion animals with chronic diseases, such as CHF, CKD, and cancer. However, this is an area that has only recently begun to be studied in dogs and cats, and much additional information is needed.

The weight loss that occurs in cachexia is unlike that seen in a healthy animal that loses weight.\(^3\) In a healthy animal that is receiving insufficient calories to meet requirements, metabolic adaptations allow fat to be used as the primary fuel source, thus preserving LBM (Fig 1). Conversely, acute and chronic diseases alter concentrations of a variety of mediators (eg, inflammatory cytokines, catecholamines, cortisol, insulin, glucagon), which then decrease the ability to make metabolic adaptations required to switch to fat utilization, and amino acids continue to be used as a primary source of energy.\(^3\)\(^,\)\(^5\) Therefore, muscle and LBM quickly are catabolized.\(^5\) Although there are some subtle differences among forms of cachexia in different human diseases (eg, cardiac cachexia versus cancer cachexia), loss of LBM is a hallmark of cachexia. Fat and bone also are lost in illness or injury to lesser degrees, although in advanced cases of cachexia, depletion of all body compartments is apparent. Studies in dogs and cats are needed to better define the alterations that occur in metabolic fuels and body compartments that occur in cachexia.

**Clinical Implications**

In people, the loss of LBM has direct and deleterious effects on strength, immune function, wound healing, and survival.\(^6\)\(^,\)\(^8\) In fact, cachexia is an independent predictor of survival in people.\(^6\)\(^,\)\(^7\) The specific deleterious effects of muscle loss have not been as well studied in dogs and cats although there are studies associating thin body condition with decreased survival.\(^9\)\(^,\)\(^11\) In 1 study of dogs with CHF with \(n = 10\) and without \(n = 9\) cardiac cachexia, cachexia was associated with alterations in hemoglobin and hematocrit, as well as CD4\(^+\) and CD8\(^+\) lymphocytes, similar to immunological changes in people with cachexia (Freeman, LM and Rush JE; unpublished data). Many of the other effects of cachexia that have been documented in people and are anecdotally identified in dogs and cats with cachexia, such as weakness, anorexia, weight loss, and perceived poor quality of life, are major contributing factors to an owner’s decision of euthanasia.\(^12\) Therefore, cachexia may play an even more important role in survival for dogs and cats because of the option for euthanasia. These important deleterious clinical implications underscore the importance of early identification and effective treatment.

**Diagnosis of Cachexia and Sarcopenia**

One of the most pressing needs in the area of cachexia research for both people and companion animals is the need for an accurate definition and a clinically relevant way to diagnose this syndrome. Current definitions in people rely primarily on loss of body weight. Total weight loss is an insensitive measure of muscle loss, and using weight loss as a diagnostic criterion decreases the ability to identify cachexia until its more advanced stages and results in underdiagnosis of this syndrome. In addition, in certain types of cachexia (eg, rheumatoid cachexia, cardiac cachexia with fluid accumulation), weight loss is masked by accumulation of fat or water. Therefore, waiting until weight loss occurs often prevents an early diagnosis and misses the important hallmark of muscle loss.

In addition to the insensitivity of weight loss as the criterion for cachexia, it is not only the quantitative loss of muscle that results in deleterious effects. There are also qualitative changes in muscle function. This has been best studied in people and rodent models of cardiac cachexia in which skeletal muscles have increased collagen content, altered mitochondrial function, and a shift from type I (oxidative) to type IIb (glycolytic) fibers.\(^13\)\(^,\)\(^14\) This shift may further predispose muscle fibers to atrophy because glycolytic fibers are less resistant to atrophy.\(^13\)\(^,\)\(^14\)

Another argument for using factors other than total weight loss for a diagnosis of cachexia is that cachexia is a process (ie, a loss of LBM) and not necessarily an end-stage syndrome. LBM loss occurs before substantial weight loss can be detected. If loss of LBM were used as a criterion for the diagnosis of cachexia, the prevalence of this syndrome in chronic diseases would be even higher. It is easy to recognize cachexia in a person or dog with advanced CHF or cancer. However, identification of cachexia is more difficult in its earlier stages when it is more subtle. The challenge is to detect cachexia at an earlier stage requires evaluation techniques that currently are not clinically applicable. Even some of the research tools that are used, such as dual-energy x-ray absorptiometry (DEXA), have limitations for measurement of LBM because of inherent assumptions (eg, constant hydration of lean tissues) that are not applicable in

![Fig 1.](image-url)
conditions associated with fluid accumulation or dehydration. Clinically applicable, precise, and accurate measures of LBM are needed to best study this syndrome and be able to treat it in the clinic.

The definition of cachexia for people is being actively debated but is not yet completely resolved. A consensus definition was developed from a meeting in late 2006 and was recently endorsed by a special interest group: “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 wasting disease.”17,18 The proposed diagnostic criteria for cachexia are listed in Table 1. The special interest group addressed the importance of diagnosing and treating cachexia at an early stage by adding a definition for precachexia (Table 2), although this definition still, unfortunately, includes weight loss as a required criterion.18 A recent consensus statement on definition and classification of cancer cachexia made the advance to require weight loss or muscle loss in the criteria for definition.

The term sarcopenia was coined by Rosenberg in 1988 but there continue to be challenges and debates surrounding the definition of sarcopenia, as with cachexia. The current definition of sarcopenia in people is proposed by the European Working Group on Sarcopenia in Older People as “a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse clinical outcomes such as physical disability, poor quality of life and death.”20 An international special interest group proposed the diagnostic criteria for sarcopenia as: (1) “a low muscle mass, i.e. a percentage of muscle mass \( \geq 2 \) standard deviations below the mean measured in young adults of the same sex and ethnic background” and (2) “low gait speed, e.g. a walking speed below 0.8 m/s in the 4-m walking test.”18 Additional research will be required to develop practical methods for measuring muscle loss in various breeds of dogs and cats. For assessing the functional aspect of sarcopenia, measures such as the 6-minute walk test, recently described in dogs, may prove to be useful.21

### Specific Forms of Cachexia

The hallmark of all forms of cachexia is muscle loss with functional deficits. However, the different forms of cachexia do have some unique features which will be described in more detail.

**Cardiac Cachexia.** Cardiac cachexia is the form of cachexia that has been longest recognized and best studied. CHF is a common disease in people, and although many advances have been made in recent years, the prognosis remains poor. In addition to the hemodynamic and neurohormonal alterations in CHF, the loss of LBM that typically accompanies this disease has devastating implications for the patient. Depending upon the definition used, cachexia has been identified in up to half of all people with CHF. In 1 study of dogs, over 50% of dogs with dilated cardiomyopathy (DCM) and CHF had some degree of cachexia.22 The presence of cardiac cachexia, even using the relatively insensitive measure of weight loss, confers an increased risk for death in people.6,7 In addition, cachexia increases morbidity and adversely affects quality of life. Thus, it is a syndrome of substantial clinical and economic importance. An excellent systematic review of cardiac cachexia recently was published.3

The deleterious effects of cardiac cachexia have been emerging, and recent studies have emphasized the role of body weight and body composition in heart failure. Whereas obesity is a risk factor for development of heart disease in people, obesity actually may be associated with a protective effect once heart failure is present—this is known as the obesity paradox.23 This is a relatively recently identified phenomenon but the evidence has rapidly grown. A recent large meta-analysis on body condition, which included over 28,000 people with heart failure, concluded that obesity and overweight were associated with lower all-cause and cardiovascular mortality and that underweight patients consistently had a higher risk of death.23 There are a number of hypothesized reasons for the obesity paradox, such as beneficial effects of medications used to treat comorbidities in obese people, cardioprotective effects of adipose tissue-derived adipokines, or a “healthier” obese population.23 However, the benefit of obesity in CHF is likely due more to a lack of cachexia, rather than to the obesity per se, given the adverse effects associated with cachexia. This is because of the increased reserve of LBM in overweight

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### Table 1. Proposed definition of cachexia in people.17

<table>
<thead>
<tr>
<th>Weight loss of at least 5% in 12 months or less (or body mass index &lt; 20 kg/m²) plus 3 of the 5 features:</th>
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<tbody>
<tr>
<td>1. Decreased muscle strength</td>
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<tr>
<td>2. Fatigue</td>
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<tr>
<td>3. Anorexia</td>
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<tr>
<td>4. Low fat-free mass index</td>
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<tr>
<td>5. Abnormal biochemistry</td>
</tr>
<tr>
<td>a. Increased inflammatory markers (C-reactive protein &gt;5.0mg/dL, interleukin-6&gt;4.0pg/mL)</td>
</tr>
<tr>
<td>b. Anemia (hemoglobin&lt;12g/dL)</td>
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<tr>
<td>c. Low serum albumin concentration (&lt;3.2g/dL)</td>
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### Table 2. Proposed definition of precachexia in people.18 All of the following 4 criteria must be met.

| 1. Underlying chronic disease |
| 2. Unintentional weight loss ≤ 5% of usual body weight during the last 6 months |
| 3. Chronic or recurrent systemic inflammatory response |
| 4. Anorexia or anorexia-related clinical signs |
and obese people, which may provide a greater reserve during the catabolic state of CHF.

A similar obesity paradox also has been demonstrated in both dogs and cats with CHF. Dogs with CHF that gained body weight had longer survival times compared with those that lost or maintained weight. In cats with CHF, cats with low body weights had shorter survival times compared with cats with moderate or high body weights. These data emphasize the importance of avoiding weight (and muscle) loss in dogs or cats with CHF by careful attention to both the medical and nutritional aspects of their care.

Cardiac cachexia typically is recognized only after CHF has developed. Loss of LBM is most readily evident in the epaxial, gluteal, scapular, or temporal muscles. Typically, the epaxial muscles over the thoracic and lumbar region are the sites in which muscle loss can be identified in its earliest stages (Fig 2). Anecdotally, dogs appear to be quite variable in the degree to which they show temporal muscle wasting. In some dogs, temporal muscle wasting is apparent at an early stage of CHF, whereas in other dogs, moderate to severe muscle wasting is present elsewhere before substantial temporal muscle wasting is apparent. It is also the author’s clinical impression that dogs often have more substantial muscle wasting compared with cats with a similar stage of CHF. Dogs with right-sided CHF have more advanced muscle loss compared with dogs with left-sided CHF.

Cancer Cachexia. In people, cancer is one of the most common diseases in which cachexia is present. In people with cancer, it is estimated that over 50% lose weight unintentionally, although the prevalence depends on the type of cancer. In 1 study of dogs with cancer, only 4% had a low body condition score (BCS ≤ 3/9) at the time of diagnosis and 55% had a BCS ≥ 6/9. Similar findings were seen in a study from 2007 in which 5% of dogs with cancer had a BCS < 4/9. However, the study by Michel et al found that 69% of dogs for which prediagnosis body weights were available had experienced some weight loss (31% had <5% weight loss, 14% had lost 5–10%, and 23% had weight loss of >10%). In addition, although BCS was low in only a minority of cases, 35% of dogs had mild to severe muscle wasting. A study in cats with cancer showed muscle loss in 91% of affected cats. In addition, cats that were below optimal body condition had a significantly shorter survival time compared to those with a BCS ≥ 5. This underscores the importance of assessing not only BCS (which assesses fat stores) but also muscle condition score (MCS; see below) and changes in body weight to detect cancer cachexia.

Renal Cachexia. The prevalence of cachexia in people with CKD is estimated to be 20%. Although the prevalence of cachexia in dogs and cats with CKD has not specifically been measured, it appears to be relatively high and likely has negative clinical effects. As in CHF, the obesity paradox, in which people who are overweight or obese have improved survival compared with those who are normal or underweight, also exists in people with CKD. The results of a recent retrospective study in 100 dogs with CKD (International Renal Interest Society stages II–IV) showed that dogs classified as underweight at the time of diagnosis had a significantly shorter survival time compared to both moderate and overweight dogs. This suggests that the obesity paradox exists in dogs with CKD, as it does in people with CKD and dogs and cats with CHF.

Other Forms of Cachexia. There are a variety of other diseases associated with cachexia in people, including rheumatoid arthritis, COPD, and AIDS. In dogs and cats with chronic respiratory diseases, clinicians often anecdotally note muscle loss. Further study is warranted in these and other diseases seen in dogs and cats.

Sarcopenia

Although 2/3 of older Americans are overweight or obese, aging also is associated with substantial loss of LBM, whether or not obesity is present. Sarcopenia is similar to cachexia in that it is characterized by muscle loss, but it is a syndrome seen during aging in the absence of disease (this is crucial to the definition of sarcopenia because LBM loss associated with disease would be referred to as cachexia). Although sarcopenia is associated with aging, it actually begins early in life, around 30 years of age, and from 20 to 80 years of age, there is a 30% reduction in muscle mass. In sarcopenia, the loss of LBM often is accompanied by an increase in fat mass so the total weight may not change (or may even increase), thus masking the sarcopenia. Sarcopenia is most commonly identified in people with computed tomography (CT) of the mid-thigh. From CT, it is apparent a person’s body

weight and external features may not reflect the loss of LBM occurring (Fig 3). Like cachexia, sarcopenia is associated with increased mortality and also has important effects on strength (which negatively impacts frailty and contributes to falls and fractures), immune function, and quality of life. The mechanism of sarcopenia appears to be multifactorial and involves physical inactivity, increased cytokine production, decreased concentrations of growth hormone and testosterone, changes in type II muscle fibers, insulin resistance, and decreased protein synthesis.

Few studies investigating sarcopenia have been conducted in dogs and cats, but available information suggests that dogs and cats also lose LBM during aging. One study of dogs using proximate (carcass) analysis reported higher mean body fat in geriatric dogs compared to younger dogs, as well as an age-related decline in total body protein. These data support the existence of a similar age-related loss of LBM as is seen in people but lacked details on breed and health of the dogs, which limits the use of these data. A study following the body weight and body composition (by DEXA) of 48 healthy Labrador Retrievers from 8 weeks of age until death identified a significant loss of LBM during aging. Another study of 40 adult Labrador Retrievers aged 2–13 years compared LBM and fat mass across age groups by DEXA and identified a negative linear relationship between age and LBM. Unfortunately, although DEXA is a feasible means of measuring body composition, it has a number of inherent limitations for measuring LBM and is not available in most clinical practices. There is less information from cats, but 1 study in cats reported little change in LBM : fat ratio with age, although only cats <10 years old were included in the study.

A recent study of healthy young (1–5 years) and geriatric (>8 years) Labrador Retrievers showed that mean epaxial muscle area measured by ultrasound and CT was significantly lower in healthy geriatric dogs compared with healthy young dogs (Hutchinson D, Sutherland-Smith J, Watson AL, Freeman LM; unpublished data). However, inflammatory mediators (C-reactive protein, tumor necrosis factor-α [TNF]) and insulin-like growth factor-1 (IGF-1) were not significantly different between groups. Thus, although sarcopenia could be identified in healthy geriatric dogs by clinically relevant techniques, differences in pathophysiological mechanisms were not found, and additional research will be needed to identify both mechanisms and potential therapeutic targets.

**Mechanisms and New Interventions**

Recent basic science studies and clinical trials in people are shedding light on the mechanisms and pathways of cachexia and sarcopenia. Although a single agent is being sought that can specifically treat or prevent these syndromes, it is becoming increasingly apparent that both cachexia and sarcopenia have highly redundant mechanisms which make single agent treatment unlikely to be successful in complete resolution. However, the multifactorial mechanisms also offer numerous potential targets for treatment. There are 4 major aspects of the pathophysiology of cachexia: increased energy requirements, decreased nutrient absorption, decreased energy intake, and alterations in metabolism.

**Increased Energy Requirements**

Depending on the underlying disease, people with cachexia may have increased energy requirements, which could contribute to the pathogenesis of the muscle loss. For example, people with CHF have increased resting energy requirements as a result of sympathetic activation, increased work of breathing, and tachycardia. However, many people with CHF
Decreased Nutrient Absorption

Decreased nutrient absorption is another possible mechanism for muscle loss in cachexia. In most diseases associated with cachexia, decreased nutrient absorption is not a clinically relevant problem. However, in people with CHF, decreased perfusion of the gastrointestinal system, bowel wall edema, and increased collagen may be present, all of which may contribute to decreased nutrient absorption. Another concern over these gastrointestinal tract changes in CHF is that they may allow translocation of endotoxin across the gut mucosa which could exacerbate systemic inflammation. The role of gastrointestinal alterations or altered nutrient absorption in animals with naturally occurring CHF has not been reported.

Decreased Energy Intake

An important problem in cardiac and other forms of cachexia is a decreased calorie intake. The anorexia may be secondary to the fatigue, dyspnea, or may be because of medication toxicity or alterations in appetite that often accompany CHF, cancer, and CKD in dogs and cats. Absolute food intake may decrease in animals with these diseases, but there also may be altered food preferences, cyclical appetite, and other issues that negatively affect overall food intake. Anorexia, for example, is present in 34–84% of dogs and cats with heart disease. Control of food intake is a complex and redundant system, and although the hypothalamus is a primary regulator of food intake, adipose tissue, the gastrointestinal tract, and nutrients themselves also play important roles. All of these factors may offer important targets for treatment of cachexia.

In health, there is a balance between factors that stimulate appetite (ie, orexigenic factors) and those that inhibit appetite (ie, anorexigenic or satiety factors). In the healthy person or animal ingesting insufficient calories to meet energy requirements, there is increased production of orexigenic stimuli and decreased production of anorexigenic factors. These changes result in increased food intake and reversal of weight loss. However, in cachexia, there is altered neural control of appetite. Although the orexigenic factors neuropeptide Y, agouti-related protein (AgRP), and ghrelin are increased, many of the satiety factors also are increased (eg, adiponectin, serotonin, insulin, pro-opiomelanocortin) or not appropriately decreased (eg, leptin). This imbalance of factors and the resistance to orexigenic signals in cachexia are primarily the result of an enhanced inflammatory state.

This dysregulation in cachexia is an important factor in decreasing food intake, and it suggests that there may be targets at which treatment can be directed to increase food intake. In evaluating new potential treatments, it will be important to ensure that they not only increase food intake and body weight, but more positively impact LBM and function. One example of a promising approach that may do both is ghrelin. Ghrelin is an endogenous ligand for growth hormone secretagogue receptor that is secreted primarily by gastric endocrine cells in response to fasting and subsequently results in increased food intake. Ghrelin modulates growth hormone secretion (and thus, IGF-1 production), stimulates neuropeptide Y and AgRP, decreases expression of pro-opiomelanocortin, attenuates cardiac and renal sympathetic tone, stimulates gastric motility, and has anti-inflammatory effects. Ghrelin concentrations are increased in people with CHF but food intake is decreased, suggesting loss of appropriate feedback and ghrelin resistance. The increased concentrations and resistance are resolved in people with CHF after cardiac transplantation. Exogenous ghrelin administration in animal models of CHF appears to overcome ghrelin resistance and results in increased weight and improved cardiac function. One small, short-term study in humans also showed increased body weight, LBM, food intake, and left ventricular ejection fraction. However, a more recent study in an induced rodent model of CHF confirmed the positive effects on body weight and LBM but found no improvement in cardiac function. Ghrelin also has shown benefits in a rodent model of CKD and in an open label pilot study of people with COPD. Use of ghrelin has been limited by its short half-life (30 minutes in people) but promising newer molecules, as well as ghrelin receptor agonists, with longer half-lives are in development.

Table 3. Selected anorexigenic (satiety) and orexigenic signals of energy homeostasis.

<table>
<thead>
<tr>
<th>Anorexigenic</th>
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<tr>
<td>Adiponectin</td>
<td>Agouti-related protein</td>
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<tr>
<td>Leptin</td>
<td>Neuropeptide Y</td>
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<tr>
<td>Pro-opiomelanocortin</td>
<td>Ghrelin</td>
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<tr>
<td>α-melanocyte-stimulating hormone</td>
<td>Endocannabinoids</td>
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<td>Insulin</td>
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<td>Serotonin</td>
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<td>Gastrointestinal hormones</td>
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<td>Serum amyloid</td>
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<tr>
<td>Serotonin</td>
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<td>Insulin</td>
<td></td>
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<tr>
<td>Pro-opiomelanocortin</td>
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In people, food intake is not only affected by the many orexigenic and satiety factors but also by physiological factors, such as social situation, memory, time of day, fatigue, depression, and hedonics. The role of these factors in dogs and cats is unknown but they likely are involved because dogs and cats appear to develop aversions to certain foods, particularly when sick, and this can contribute to decreased food intake.

**Metabolic Alterations**

Increased energy requirements, alterations in nutrient absorption, and decreased energy intake all likely play important roles in the pathogenesis of cachexia by causing a net calorie deficit. However, a healthy animal that has a calorie deficit, either as a consequence of decreased food intake or increased energy requirements, would primarily lose fat. Therefore, these factors are not sufficient to explain the muscle and LBM loss and relative sparing of fat that are the hallmarks of cachexia. This discrepancy suggests that metabolic alterations also are present.

The importance of inflammatory cytokines has been well studied in CHF. An association between cardiac cachexia and TNF was first reported in 1990. When that and subsequent studies first were published, it appeared that TNF was the major cause of this syndrome, and cachexia research throughout the 1990s focused on TNF and other inflammatory cytokines. However, as research on cardiac and other forms of cachexia has expanded, it is becoming increasingly clear that there are multiple metabolic alterations involved in the pathophysiology of cardiac cachexia and that it is a relatively redundant system with multiple pathways triggering the muscle loss. However, at the core of cachexia is an altered protein flux (ie, decreased protein synthesis or increased protein catabolism) resulting in a net loss of lean tissue.

**Inflammatory Cytokines**

The inflammatory cytokines, especially TNF, interleukin-1β (IL-1), and interleukin-6 (IL-6), are primary factors in cachexia because they cause anorexia, increase energy metabolism, and accelerate loss of LBM. TNF and IL-1 also cause cardiac myocyte hypertrophy and fibrosis and have negative inotropic effects that may contribute to progression of the underlying disease. Their mechanism appears to be primarily through the nuclear factor-κB (NF-κB) pathway, which has numerous effects, including increased muscle proteolysis, down-regulation of the myogenic genes myoD and myogenin, decreased muscle regeneration, and inhibition of muscle differentiation. Identification of the central role of TNF in cachexia in the early 1990s prompted enthusiasm for anti-TNF treatments (eg, soluble TNF receptors, TNF antibodies). These compounds showed great promise in rodent models as well as in Phase I and II clinical trials in people for improving heart disease and attenuating muscle loss. However, when taken to Phase III clinical trials for CHF, not only did they prove to be unsuccessful, but lack of efficacy or increased mortality actually prompted their early cessation. These TNF antagonists have proven to be beneficial in certain diseases in people, such as rheumatoid arthritis and Crohn’s disease, where drugs such as etanercept and adalimumab are used regularly and appear to have positive effects not only on the underlying disease but also on muscle mass. However, TNF antagonists for people list a warning for new or worsening heart failure. Blockade of TNF or other inflammatory cytokines still may have benefits in some forms of cachexia, but enthusiasm over this approach has been substantially tempered. Inflammatory cytokines also are increased in dogs and cats with CHF. The effects of blocking TNF or other inflammatory cytokines in dogs and cats are unknown but there are greater challenges given the species-specific nature of these antibodies.

Complete blockade of TNF or other inflammatory cytokines may have adverse effects in cardiac cachexia, but partial blockade of cytokines may provide multiple benefits both for the underlying disease and the muscle loss. Omega-3 fatty acids decrease inflammatory cytokines and have been shown to have benefits on muscle mass in dogs with cardiac cachexia. Even some medications used to treat cardiac disease have modest anticytokine effects (eg, angiotensin converting enzyme [ACE] inhibitors, beta-blockers, amiodarone, levosimendan). Additional research on the noncardiovascular effects of these drugs in animals with cardiac and other forms of cachexia is warranted.

One of the challenges in studying inflammatory cytokines in companion animals is the relative unavailability of species-specific antibodies and commercial ELISAs, compared to the wide array available for humans and rodent models. Although a commercial canine-specific TNF ELISA is now available, other companies are marketing rodent or human-specific assays or methodologies as being “validated” in dogs. Investigators should carefully evaluate these products or techniques before using them.

**Ubiquitin-Proteosome Pathway**

Recent research has helped delineate the cell signaling pathways involved in the effects of TNF and IL-1 on cachexia. This enhanced understanding of the pathways is helping identify more specific, more effective, and safer targets for treatment. There are multiple proteolytic pathways, but the most important one in cachexia appears to be the ubiquitin-proteosome pathway. This pathway is primarily activated by NF-κB which is, in turn, stimulated by inflammatory cytokines and reactive oxygen species. The catabolic effects of glucocorticoids also appear to occur by activation of the ubiquitin-proteosome pathway. Therefore, the NF-κB pathway is the final common pathway for a variety of mechanisms involved in cachexia. Some of the signaling pathways activated by NF-κB that cause ubiquitination and mediate proteosome-dependent
protein degradation in cachexia include muscle-specific E3 ligases, MAFbx/atrogin-1, and MuRF1.84

The ubiquitin-proteosome pathway also can induce cachexia through both NF-κB-dependent and NFκB-independent pathways via myostatin.85–87 Myostatin is a member of the transforming growth factor beta (TGF-β) super-family that negatively regulates skeletal muscle mass.87 Myostatin concentrations are decreased by exercise training, allowing muscles to increase in size.85 A number of myostatin mutations have been described in various species in which enlarged musculature is present.88–93 This may be desirable in cattle (double muscled cattle breeds, such as the Belgian Blue and Piedmontese),88–90 sheep (Texel sheep),91 or racing whippets (“bully” whippets which have increased racing speed),92 or it may have no clear benefits, as in a boy with a myostatin mutation who could lift unusually heavy weights at the age of 4.92

Myostatin has been shown to be increased in animal models and people with CHF and is upregulated in both skeletal and cardiac muscle.85,87,89 One study in a rodent model showed that myostatin administration replicated the muscle loss seen in cachexia and sarcopenia.95 TNF appears to be one of the signals for increased myostatin expression via NF-κB but other factors, such as angiotensin II, also increase myostatin expression.85–87 This upregulation appears to contribute to the muscle loss in CHF. Myostatin knock-out mice with induced heart disease did not exhibit muscle loss, suggesting that blocking myostatin may be beneficial in cachexia.96 To date, myostatin antagonism has received the most study in cancer cachexia, where benefits on maintaining muscle mass have been documented in rodent models.97–99 Myostatin antagonism also decreased muscle loss in a rodent model of sarcopenia.100 Human clinical trials currently are underway to study the effects of myostatin inhibitors in sarcopenia and muscular dystrophy. Exercise training also may be a method of decreasing myostatin concentrations.85

Neurohormonal Activation

The NF-κB pathway appears to play a role in cachexia through multiple mechanisms, but it is not the only means by which muscle loss occurs. Neurohormonal activation also may contribute to muscle loss, particularly in the case of cardiac cachexia in which a wide range of neurohormonal alterations occur that can affect myocardial and whole body energy metabolism and protein flux. Catecholamines and neurohormones (eg, renin-angiotensin-aldosterone system, epinephrine, cortisol) can increase catabolism.5 Beta-blockers were shown to decrease protein oxidation and muscle atrophy in a rodent model of CHF.101 and at least 2 studies in people with cardiac cachexia also have shown benefits of beta-blockers.102,103 Atrial natriuretic factor (ANP) increases lipolysis, and a recent study showed that B-type natriuretic peptide (BNP) and ANP both were higher in people with cardiac cachexia, and there was a correlation between these polypeptides and TNF.104,105 Although the natriuretic peptides may have benefits in CHF through their natriuretic effects, their net effects on weight and muscle loss appear to be negative.106 ACE inhibitors also may have some benefits for preventing cardiac cachexia, partly because of their cardiovascular effects, but also because of direct effects on muscle, such as improved muscle oxidative capacity and capillary density, as well as decreased inflammation.5,107

Adipokines

Adipocytes once were considered inert cells with purely structural activities. However, they are now known to be metabolically active cells that elaborate adipokines such as leptin, adiponectin, and resistin. Adiponectin, in particular, is the adipokine found in highest concentrations in the adipocyte and has been shown to have anti-inflammatory effects and to decrease body weight. Research on adipokines is now being carried out in people and dogs with CHF and cardiac cachexia.8–108–110 People with cardiac cachexia have higher adiponectin concentrations than those without cachexia but leptin is not different between groups (after adjusting for fat mass).108,109 Adiponecin correlates with NT-pro BNP, exercise capacity, and survival.109,111 Two recent studies found increased concentrations of leptin and decreased concentrations of adiponectin in dogs with CHF, but the association between cachexia and adipokines has not been evaluated.8,110 Adipokine concentrations in people with cancer cachexia appear to be more variable and may be related to different tumor types.112–114

Anabolic Agents

Increased protein catabolism is a major contributor to cachexia. However, the other side of the protein flux equation (ie, decreased protein synthesis) also may play a role in causing a net loss of lean tissue. Growth hormone and IGF-1 play critical roles in the maintenance of normal muscle mass. IGF-1 mediates most of growth hormone’s actions. Inflammatory mediators, such as TNF, impair the effects of IGF-1, suggesting an important role in the pathogenesis of cachexia.115 Circulating IGF-1 concentrations also are an independent predictor of survival in people and dogs with CHF.22,116 Results from studies in rodent models of CHF showed growth hormone resistance, and growth hormone treatment in CHF and aging has not proven to be overwhelmingly successful and has important adverse effects.117 However, some promising results have been obtained in studies evaluating IGF-1 treatment in rodent models of cachexia.115,118 IGF-1 may offer an effective method for treatment of cachexia and sarcopenia in the future. Stimulation of IGF-1 production by other methods, including nutritional approaches and resistance training, also may be possible.119
Testosterone also has anabolic effects on skeletal muscle, but its adverse effects limit its use in cachexia and sarcopenia. However, nonsteroidal selective androgen receptor modulators (SARMs) are being developed for use in cancer cachexia and possibly other forms of cachexia and sarcopenia. The benefit of SARMs is that their anabolic activity is primarily limited to muscle and bone and they have minimal androgenic effects in other tissues, thus decreasing adverse effects. At least 1 SARM (Ostarine or MK-2688) has currently is in clinical trials for people with cancer cachexia and may have value in other forms of cachexia and sarcopenia as well.

New Pharmacologic Interventions for Cachexia and Sarcopenia

Because of the important implications of cachexia and sarcopenia on morbidity and mortality in people, there is now extensive research into the prevention, diagnosis, and treatment of these syndromes. There are exciting opportunities for new and effective targets to decrease energy requirements, enhance energy intake, improve nutrient absorption, and modify metabolic alterations to prevent and even reverse the effects of both cachexia and sarcopenia. The results of most studies suggest that blocking single pathways may not be completely effective; treatments that have multiple effects may prove most valuable. For example, ghrelin improves food intake but also increases growth hormone and may have direct beneficial effects on the heart. These multiple effects can be exploited to address the multiple pathways affected in this syndrome. At this time, few of these interventions have been studied in companion animals, but the burgeoning interest in these syndromes in people is likely to result in the development of products that may have benefits in animals or may spur interest in the veterinary pharmaceutical industry.

Effective pharmacologic treatments not only need to increase body weight, but need to specifically increase LBM. Because there are both quantitative and qualitative changes in muscle in cachexia and sarcopenia, measures of muscle function (eg, hand-grip dynamometry, leg extension strength, 6-minute walk test) in addition to the amount of LBM may be clinically relevant. Some of these tests used in people (eg, 6-minute walk test) also may prove to be valuable for assessing dogs. These factors also may be important in assessing effectiveness of treatments. It also is becoming clear that, to be most effective, a treatment for cachexia must have 3 different but complementary effects: (1) an anticatabolic effect to decrease muscle loss, (2) an anabolic effect to enhance protein synthesis, and (3) adequate substrate to support the first 2 actions (ie, calories, protein, and other nutrients). Treatments with anabolic effects, for example, will not be effective if there is insufficient substrate with which to perform anabolism. Therefore, careful attention to the nutritional aspects of treatment of cachexia and sarcopenia is critical for success.

Nonpharmacologic Interventions for Cachexia and Sarcopenia: Practical Implications for the Veterinary Clinician

Although promising new pharmacologic approaches to prevent and treat cachexia and sarcopenia are being developed, they are not yet available for clinical use in people or companion animals. However, in the meantime, the veterinary clinician still can address these 2 important syndromes in dogs and cats.

Diagnosis: The Importance of Enhanced Clinician Awareness

One of the keys to the management of cachexia and sarcopenia in dogs and cats is recognizing it in its earliest stages. To achieve this, BCS and MCS must be consistently assessed. The goal for BCS in a healthy dog or cat is 4–5 on a 9-point BCS scale. However, in certain diseases (eg, CHF, CKD), a slightly higher BCS may be desirable (ie, a BCS of 6–7/9), although further research is required to make specific recommendations. Even in animals with these diseases, obesity (BCS > 7/9) should be avoided.

The MCS differs from the BCS in that it specifically evaluates muscle mass. Evaluation of muscle mass includes visual examination and palpation of the head, scapulae, epaxial muscles over the thoracic and lumbar vertebrae, and pelvic bones. BCS and MCS are not directly related because an animal can be obese but still have substantial muscle loss (or conversely be very thin but have a normal MCS). Palpation is required for accurately assessing BCS and MCS, especially in animals with medium or long hair coats.

Cachexia should be anticipated in animals with chronic diseases such as CHF, CKD, cancer, and others. Consistently evaluating MCS in all patients will help identify muscle loss at an early, mild stage in aging or ill animals, rather than waiting until muscle loss is moderate or severe, when it may be more difficult to successfully manage. Similarly, as animals age, muscle loss is likely to occur, even in healthy individuals. Therefore, muscle mass should be thoroughly evaluated in geriatric cats and dogs.

Nutrition

For animals with chronic diseases in which weight or muscle loss is a component (eg, renal, cardiac, or hepatic failure; cancer; respiratory disease), it is critical to optimize medical treatment for the underlying disease. Specific recommendations for optimal diet (which includes the primary pet food, as well as treats, table food, and foods used for medication administration) should be an integral part of the overall medical treatment for all chronic disease conditions. In many cases, practical methods to help owners manage their animal’s appetite are critical to success. This is particularly important because anorexia is one of the most common contributing causes to an owner’s decision to euthanize his or her pet. Dietary modification, assisted
feeding, or other feeding strategies often are beneficial in improving food intake and quality of life for these patients.

Any issues that potentially can affect food intake should be addressed, whether physical or environmental. Dental disease, for example, can substantially impair food intake in an otherwise healthy or sick animal. Pain (eg, back or joint) can decrease an animal’s mobility and make it more difficult to secure adequate food intake. Environmental issues also can negatively impact food intake. Multipet households may impede the ability of an individual animal to gain access to food (eg, a more frail or timid animal may be crowded out from the food bowl). Stress often can increase for animals after diagnosis of cancer or CHF because of lifestyle changes (eg, medication administration, new foods), as well as increased stress on the part of the owner, which may be detected by the animal. An excellent website on environmental issues for dogs and cats is available for veterinarians and owners.123

In addition to underlying medical issues and important environmental factors, the diet should be carefully evaluated. A brief nutrition screening should be performed in every patient at every visit, including a diet history, BCS, and MCS.121,122 For animals that have risk factors identified from the screening (eg, animals with medical conditions, geriatric animals, and those with altered BCS or MCS), a more thorough nutrition evaluation is required.121,122 The diet history often reveals important information that can then provide relatively easy, practical solutions. Clinicians should ensure that the diet being eaten by the animal is nutritionally complete and balanced. If owners are feeding a homemade diet, it is almost always nutritionally unbalanced (sometimes severely so) unless the diet was formulated by a board-certified veterinary nutritionist and the owner is carefully following the recipe. Even commercial dog and cat foods may be nutritionally unbalanced if the food label states “for intermittent or supplemental use only.” This is acceptable for veterinary therapeutic diets that are designed specifically to help manage diseases and are used under the supervision of a veterinarian. However, an over-the-counter diet should always be complete and balanced if it is fed in any substantial amounts to a dog or cat. In the United States, nutritional adequacy statement on a diet that is complete and balanced will be worded either as “(Name of product) is formulated to meet the nutritional levels established by the AAFCO [Association of American Feed Control Officials] Dog (or Cat) Food Nutrient Profiles” or “Animal feeding tests using AAFCO procedures substantiate that (Name of Product) provides complete and balanced nutrition for ...” (label regulations vary according to country).124 Over-the-counter diets that are not nutritionally balanced may contribute to muscle loss (in a healthy or sick animal) and should be avoided. These diets also may not have an optimal nutritional formulation for the animal’s underlying disease (eg, protein, fat, sodium, phosphorus).

The diet history also may reveal that the diet is unbalanced not because the animal is eating an unbalanced commercial food, but because of intake of a large proportion of calories from treats, rawhides, or “people food.” In this situation, even if the main diet is well-balanced, the other foods may be fed in a large enough proportion that the overall diet is unbalanced, which can contribute to weight and muscle loss as well as not being optimal for the underlying disease.

Determining the specific brand and flavor of the animal’s main diet is important because it may reveal other factors that can contribute to cachexia or sarcopenia. For example, animals may be eating a diet that is relatively low in protein which will not be sufficient to maintain muscle mass in an animal with increased protein catabolism. Animals with CHF should not be fed a renal or otherwise reduced protein diet unless advanced concurrent CKD is present. Providing at least the AAFCO minimum for protein (5.1 g/100 kcal for dogs and 6.5 g/100 kcal for cats)124 is important, although higher dietary protein levels may be more optimal. Senior diets are highly variable in terms of their protein content (4.8–13.1 g/100 kcal for commercial senior dog foods in one study).125

Commercial dog and cat foods also vary widely in calorie density, and because calorie information is not currently required on pet food labels (except for light or reduced calorie foods), it can be difficult for owners to realize that they may be inadvertently increasing or decreasing the daily calorie intake of their pets when they change from one food to another. One study found that the calorie density of senior dog foods ranged from 246 to 408 kcal/cup,125 and there are adult dog and cat foods available on the market now that are >600 or <250 kcal/cup. Therefore, it is important to ensure that undesired weight loss is not simply the result of switching to a lower calorie density food. It is also useful to be aware that senior diets not only vary in calorie density, but also in other nutrients that may be of importance in various diseases, including CHF and CKD. The sodium content in 37 senior dog foods, for example, ranged from 33 to 412 mg/100 kcal (the AAFCO minimum for sodium in dog foods is 20 mg/100 kcal).125

Dietary supplement use is important to determine. Animals with diseases are more likely to be receiving supplements,160,61,126 but owners typically do not volunteer this information unless specifically asked. Dietary supplements may contribute to muscle loss by causing anorexia or other adverse effects or by interacting with medications used to treat the underlying disease, thus decreasing their efficacy or increasing the adverse effects of the medications.

The preceding information emphasizes the importance of obtaining and evaluating a thorough diet history in animals with cachexia or sarcopenia. Board-certified veterinary nutritionists can be helpful in assisting the busy veterinary clinician by consultations in these situations.127,128
Anorexia: Addressing Changes in Appetite

One of the most important issues for managing the anorexia that is often associated with cachexia and sarcopenia is to optimize medical treatment. However, appetite can remain a challenging issue despite optimal treatment of the underlying disease. Complete anorexia may not be present but owners often note changes in appetite, such as reductions in food intake, changes in food preferences, or “cyclical” appetite (ie, the animal will eat one food well for several days or weeks and then refuse it). A reduction in food intake in an animal that previously has been eating well may be an early sign of worsening of the underlying disease or a need for medication adjustment.

To address decreased food intake, client communication is important. Owners who are prepared for changes in appetite, both amounts and types of food, appear better able to deal with these changes effectively. The author typically provides a list (and samples) of several different commercial foods that meet the animal’s nutritional needs based on the underlying disease and individual characteristics (eg, clinical signs, physical examination findings, laboratory results, and the individual animal and owner preferences). The owner then is instructed to feed one of the foods but to keep the others in reserve to try if appetite for the first food fails (although the animal often will eat that food again later). A nutritionally balanced, home-cooked diet formulated by a veterinary nutritionist also is an option, although these may be better reserved for later stages of disease to maintain more options as the disease progresses. Smaller, more frequent meals also may increase food intake, as can flavor enhancers (foods added to the dog or cat food to increase palatability). Flavor enhancers must be tailored to the disease (eg, high sodium flavor enhancers should be avoided in CHF, and high phosphorus and protein flavor enhancers, such as meat, fish, or cheese should be avoided in CKD). Cats typically prefer meat or fish type flavors, whereas dogs are more variable, with some preferring meat flavors and others preferring sweet flavors, such as yogurt, maple syrup, or applesauce. Animals with chronic diseases and even healthy aging animals often appear sensitive to food temperature and may have specific preferences. Thus, experimentation with foods at different temperatures may be helpful. Cats often prefer foods warmed but dogs may prefer food warmed, at room temperature, cold, or even frozen. Feeding the animal on a dinner plate, rather than the usual pet food bowl, or feeding in a different place in the house also may increase food intake. Modulation of cytokine production also can be beneficial for managing cachexia. Supplementation of the diet with fish oil, which is high in omega-3 fatty acids, can decrease inflammatory cytokine production and improve cachexia and food intake (see below).22

Appetite stimulants (eg, mirtazapine, cyproheptadine) may benefit some animals with decreased or altered appetite, but it is important to carefully monitor body weight, BCS, MCS, and food intake to ensure adequate calorie intake. Owners (and veterinarians) often are mollified by some food intake, even if it is not sufficient to maintain weight or is not comprised of optimal diets or dietary components (eg, a cat with CKD that will only eat meat or a high protein, high phosphorous commercial food). In animals that continue to lose weight and muscle, despite the tactics suggested above, a feeding tube should be considered. Early tube placement is preferable to, and typically has a better outcome, than waiting until the animal is in end-stage disease with severe debilitation.

Omega-3 Fatty Acids

Increased dietary long-chain polyunsaturated omega-3 fatty acids, either from a highly enriched diet or through supplements, may have a number of benefits in animals with diseases that predispose them to cachexia or in animals with sarcopenia. Omega-3 fatty acids result in less potent inflammatory mediators (eicosanoids) than do omega-6 fatty acids, and omega-3 fatty acids also decrease TNF and IL-1 production. Omega-3 fatty acid supplementation has been shown to decrease the muscle loss in dogs with CHF and, in some animals, to improve appetite.22 In cardiac disease, omega-3 fatty acids have antiarrhythmic effects and also may enhance myocardial energy metabolism.129,130

The optimal dosage of omega-3 fatty acids has not been determined, but the author currently recommends a dosage of fish oil to provide 40 mg/kg/day eicosapentaenoic acid (EPA) and 25 mg/kg/day docosahexaenoic acid (DHA) for animals with any degree of cachexia. Unless the diet is one of a few specially designed therapeutic diets, supplementation will be necessary to achieve this omega-3 fatty acid dosage. When recommending a supplement, it is important to know the exact amount of EPA and DHA in the specific fish oil brand because supplements vary widely. Fish oil supplements with good quality control should be used and they should always contain vitamin E as an antioxidant, but other nutrients should be excluded to avoid toxicities. Cod liver oil should not be used to provide omega-3 fatty acids at this high dose because it contains high concentrations of vitamins A and D which can result in toxicity. Flax seed oil or other plant-based omega-3 fatty acids also should be avoided because inefficient hepatic elongation of α-linolenic acid to EPA and DHA makes these inefficient (in dogs) or ineffective (in cats) sources of omega-3 fatty acids for these species.131 In addition, ventricular arrhythmias in dogs were not significantly decreased by flax seed oil supplementation, as they were with fish oil.129

Exercise

Exercise has been an effective method for helping to maintain muscle mass in people with cachexia and
sarcopenia. There are differential effects of aerobic and resistance exercise in people. Although both have some benefits, resistance exercise appears to be particularly useful. For example, resistance training increases muscle mass in people but also can normalize some of the alterations seen in cachexia, such as reduced GLUT4 expression and increased myostatin concentrations. Exercise may be more challenging in some of the diseases associated with cachexia in dogs (eg, CHF) and particularly in cats, but exercise such as walking may provide an effective treatment for muscle loss in some diseases and in preventing sarcopenia in aging animals. Developing methods of resistance training for animals, such as electrical stimulation of the muscles, also may be beneficial.

**Conclusion**

Sarcopenia and cachexia are becoming important in veterinary practice because of their high prevalence and deleterious effects, and a better understanding of these syndromes is critical to optimize patient care. The aging population, increased diagnosis of diseases, such as CHF, cancer, and CKD, and an increasing willingness of owners to pursue treatment are expanding the number of dogs and cats that would benefit from treatment. New drugs, nutritional approaches, and other treatments to specifically target sarcopenia and cachexia are being developed and are likely to benefit dogs and cats, as well as people. Veterinarians should be aware of cachexia and sarcopenia and their negative effects on animals, because earlier diagnosis will provide enhanced opportunities for treatment. Cachexia has been recognized for centuries, and solving this challenge will not be simple in people or companion animals. However, as the pathophysiology continues to be better understood, effective treatments to address the identified targets will be developed and hopefully benefit the large number of companion animals with these syndromes.

**Footnotes**

8Society on Sarcopenia, Cachexia, and Wasting Disorders, http://www.cachexia.org
13Quantikine tumor necrosis factor-α immunoassay, R&D Systems, Minneapolis, MN
15Ostarine (MK-2688), GTx, Inc, Memphis, TN

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