Cachexia and Sarcopenia in Companion Animals: An Under-Utilized Natural Animal Model of Human Disease

Lisa M. Freeman

Department of Clinical Sciences, Cummings School of Veterinary Medicine, Tufts University, North Grafton, MA 01536, USA

Abstract

While laboratory small animal models of cachexia and sarcopenia are well-suited and critical for studying mechanisms and early pre-clinical phases for potential treatments, they are not similar enough to the human condition to always be good predictors for results in human clinical trials. As a result, translational failures can occur when large-scale human clinical trials are conducted on drugs, even when they appear promising in pre-clinical studies in rodent models. What is needed is a way to more efficiently and successfully translate information gained from basic science and rodent research into human clinical trials that produce effective approved drugs. Naturally-occurring cachexia and sarcopenia in companion animals is a more representative model of human disease that can serve as a stepping stone between basic science and human clinical trials. Many of the common diseases of humans also affect companion animals, particularly pet dogs and cats. Pet dogs and cats commonly develop heart failure, cancer, and kidney disease, as well as acute trauma or illness. The population of elderly companion animals also is increasing as pets’ lifespans have become longer. As a result, both cachexia and sarcopenia are very common in companion animals. Studying these conditions in dogs and cats – either in colonies or in animal clinical trials – can help to identify successful treatments that can benefit both humans and companion animals.

Address for correspondence: Lisa M. Freeman, DVM, PhD, DACVN, Department of Clinical Sciences, Cummings School of Veterinary Medicine, Tufts University, North Grafton, MA 01536, USA. Tel: 1-508-887-4523, Fax: 1-508-839-7922, E-mail: Lisa.Freeman@Tufts.edu

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Introduction

The understanding of cachexia and sarcopenia has progressed rapidly in recent years, and a variety of promising new treatments for humans are being studied. This is encouraging for the more than 6-12 million people estimated to be affected by cachexia and sarcopenia worldwide [1]. However, one continuing roadblock is successful translation of basic science research and research from rodent models into effective treatments for humans with cachexia and sarcopenia. There are many induced or genetic animal models of cachexia and sarcopenia being studied, with several excellent recent reviews [2-7]. While these laboratory small animal models of cachexia and sarcopenia are well-suited and critical for studying the mechanisms and early pre-clinical phases for potential treatments, they are not similar enough to the human condition to always be good predictors for results in human clinical trials. As a result, translational failures can occur when large-scale human clinical trials are conducted on drugs, even when they appear promising in pre-clinical studies in rodent models. A recent report found that only 30.7% of candidate drugs advanced to Phase III and only 9.6% of drugs entering Phase I advanced all the way to FDA approval [8].

What is needed is a way to more efficiently and successfully translate information gained from basic science and rodent research into human clinical trials that produce effective approved drugs. Naturally-occurring cachexia and sarcopenia in companion animals is under-utilized as a more representative model of human disease that can serve as a stepping stone between basic science and human clinical trials.

Many of the common diseases of humans also affect companion animals, particularly pet dogs and cats. Common chronic diseases in dogs and cats include congestive heart failure (CHF), cancer, and chronic kidney disease (CKD). Dogs and cats also are affected by acute trauma or illness, and may be treated for days to weeks in veterinary intensive care units with most of the same facilities and care found in human ICUs. With longer lifespans, the population of elderly pets also is increasing. In all of these acute and chronic conditions affecting companion animals, cachexia and sarcopenia are common. Although weight and muscle loss have been recognized in companion animals for many years, only recently have they become acknowledged as a common and detrimental finding [9]. As a result, concerted efforts are being made to combat these conditions and to improve outcome for the wide variety
of diseases with which they are associated. At the same time, these natural large animal models of cachexia can be a valuable resource for the development of effective treatments for humans.

Most of the common diseases affecting companion animals are similar or identical to the human disease. Prevalence rates are often similar across species, such as with obesity, where the rates in dogs and cats mirror those found in humans [10]. However, diseases may be even more common in companion animals because of their selective breeding. For example, nearly 100% of one dog breed is affected by heart disease (see below) and up to 50% of one cat breed is affected by polycystic kidney disease [11]. As a result, studies of cachexia and sarcopenia can be readily conducted in companion animals, either in genetically-defined colonies of dogs or cats or through clinical trials in pet dogs and cats. In addition to the advantages of high prevalence of disease, clinical trials in companion animals can often be shorter than in humans since dogs and cats typically reach endpoints (e.g., CHF) faster than humans (Table 1). Other advantages include shorter lifespans, the ability to control nutritional and other environmental factors, and the fact that both the dog and cat whole genome sequences are publicly available and annotated. Diagnosis and treatment of companion animal diseases can be nearly identical to that of humans, with similar diagnostic tests (e.g., advanced imaging, laboratory testing, genetic testing) and treatments (e.g., medications, radiation therapy, interventional cardiology techniques, specialized surgical techniques).

More effective drugs, diets, and other treatments are needed to combat cachexia and sarcopenia across species. With an estimated 164 million pet dogs and cats in the United States [12], there are large numbers of pet dogs and cats with naturally-occurring diseases that can participate in clinical trials to bridge basic science research or rodent models and human clinical trials. This approach can reduce the all-too-common translational failures and identify novel treatments for cachexia and sarcopenia that can benefit both humans and animals. Because this approach is under-utilized, the purpose of this review is to raise awareness of the wide array of naturally-occurring animal models of cachexia and sarcopenia, and of opportunities for collaboration among clinicians and researchers.

Cachexia and sarcopenia in companion animals

Cachexia is a common condition in companion animals, occurring in a variety of chronic and acute diseases, such as CHF, cancer, CKD, chronic respiratory disease, and acute illness or injury. As in humans, the weight loss that occurs in cachexia is unlike that seen in a healthy animal that loses weight, and the primary tissue lost in cachexia is muscle and lean body mass (LBM). Although there are some differences among forms of cachexia in different diseases (e.g., cardiac cachexia versus cancer cachexia), a quantitative and qualitative loss of muscle is a hallmark of cachexia in dogs and cats. Fat and bone also are lost to a lesser degree, although in advanced cases of cachexia, all body compartments are depleted.

Like cachexia, sarcopenia is characterized by quantitative and qualitative changes in muscle, but sarcopenia occurs during aging even in the absence of disease. Cachexia and sarcopenia can occur concurrently since many chronic diseases occur in the aging population. As pet dogs and cats are living longer lives, the incidence of sarcopenia is increasing.

Clinical implications of cachexia and sarcopenia

In humans, cachexia significantly increases morbidity and mortality. The specific deleterious effects of cachexia and sarcopenia have not been as well studied in dogs and cats, although there are studies associating thin body condition with decreased survival in general populations of pet cats [13], and in a variety of diseases (see below). One issue relevant to survival that is different in companion animals compared to humans is the option for euthanasia which can impact estimates of survival time. Many of the effects of cachexia that have been documented in humans also are identified in dogs and cats with cachexia (e.g., weakness, anorexia, weight loss, and poor quality of life), and can contribute to a pet owner’s decision of euthanasia [14]. Therefore, cachexia may play an even more important role in survival for dogs and cats. These deleterious clinical implications underscore the importance of early identification and effective treatment. Like cachexia, sarcopenia is associated with increased mortality and also has important effects on strength, immune function, and quality of life in both humans and companion animals [15-17].

Diagnosis of cachexia and sarcopenia

In humans, the definition of cachexia continues to be refined but emphasizes unintended weight loss (>5% in 12 months or less), along with some combination of decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry (i.e., increased inflammatory markers, anemia, hypoalbuminemia) [18]. Even the definition of precachexia requires unintended weight loss (<5%) [19]. Although the focus on weight loss provides a clinically relevant way to diagnose this syndrome (assuming clinicians are aware of it and look for it), weight loss is an insensitive measure of muscle loss. By the time weight loss of even 5% occurs, the loss of LBM is relatively far along in the process, making intervention more difficult. Another issue is that in certain types of cachexia (e.g., rheumatoid cachexia, cardiac cachexia with edema or ascites), weight loss is masked by accumulation of fat or water. Therefore, the use of weight loss as part of the
definition of cachexia often impedes the ability to make an early diagnosis and may miss the important hallmark of muscle loss.

In veterinary medicine, the diagnosis of cachexia and sarcopenia has focused on muscle loss, rather than weight loss in an effort to diagnose these conditions at an earlier stage [9]. Weight loss can be an additional indicator of cachexia and sarcopenia but is not required for a diagnosis of either of these conditions. Other components of the human definition for cachexia are not included since inflammatory mediators are not routinely measured in clinical practice (although can be measured in dogs and cats in clinical trials or research colony situations). Assessing muscle function also is difficult since straightforward techniques, such as handgrip strength, are not possible. However, a 6-minute walk test has been used in dogs [20, 21].

Moderate to severe cachexia is not difficult to identify in a person or dog with advanced CHF or cancer (Fig 1). However, identification of cachexia in its earlier and more subtle stages can be more challenging (Fig 2), but is one of the keys to successful management of these common conditions. Body composition of companion animals can be assessed by a variety of methods (e.g., dual X-ray absorptiometry [DEXA], computed tomography [CT]), and both have been used to identify cachexia and sarcopenia in dogs and cats [9, 22]. These methods are typically not used in general clinical practice because they require general anesthesia or sedation, but are found in most universities, large referral practices, and research facilities. Therefore, more clinically applicable methods besides body weight are needed. Clinically, veterinarians cannot use body mass index due to the wide variety of shapes and sizes of different breeds (particularly in dogs). The most commonly used clinical assessment of body composition in veterinary medicine is the body condition score (BCS). This is a validated score classified on a 1-9 scale where 1=emaciated, 9=obese, and 4-5 is considered ideal [23, 24]. Body condition score is a semi-quantitative assessment of body composition focusing primarily on stores of adipose tissue.

Because the BCS provides primarily an assessment of fat stores, a separate assessment of the LBM and muscle is also important to identify cachexia and sarcopenia. A clinical method for doing so is the muscle condition score (MCS), which differs from the BCS in that it specifically evaluates muscle mass (Fig 3) [25, 26]. The MCS is based on visual examination and palpation of muscle mass over the head, scapulae, epaxial muscles over the thoracic and lumbar vertebrae, and pelvic bones (palpation is particularly important in animals because of the haircoat). Typically, the epaxial muscles over the thoracic and lumbar region are the sites in which muscle loss can be identified in its earliest stages. Dogs are variable in the degree to which they show temporal muscle wasting, and this finding is uncommon in cats. Body condition score and MCS are not directly related because an animal can be obese but still have substantial muscle loss (“sarcopenic obesity,” which may confer an even worse outcome); conversely, animals can be very thin but have a normal MCS.

Nutritional assessment guidelines for veterinarians from national and international veterinary organizations recommend assessing body weight, BCS, and MCS at every visit [27, 28]. This is valuable since even this quick assessment can readily identify cachexia and sarcopenia in pets. Cachexia should be anticipated in animals with chronic diseases such as CHF, CKD, and cancer, and in hospitalized acutely ill or injured animals. Consistently evaluating MCS in all patients will help identify muscle loss at an early, mild stage in ill or injured animals, rather than waiting until muscle loss is moderate or severe, when it is more difficult to successfully manage. Similarly, as animals age, muscle loss is likely to occur, even in healthy individuals. Therefore, the MCS should be carefully evaluated in geriatric cats and dogs.

Clinically applicable, precise, and accurate measures of LBM are needed to study cachexia and sarcopenia and to be able to treat these conditions. Recently, our group validated an ultrasound technique, the Vertebral Epaxial Muscle Score (VEMS), to more accurately quantify muscle in dogs [22, 29]. To perform this, a ratio is calculated of the maximal transverse epaxial muscle height at the level of the 13th thoracic vertebra (Fig 4) divided by the length of the 4th thoracic vertebra from thoracic radiography. The VEMS was valid and reproducible for dogs of different sizes and body conformations. A similar method is being developed for cats. These methods will be valuable for earlier detection of cachexia and sarcopenia, as well as for quantitative outcome measures in studies of potential treatments for these conditions.
A dog with advanced cardiac cachexia secondary to naturally-occurring dilated cardiomyopathy and congestive heart failure. Note the severe muscle loss over the head, scapulae, epaxial muscles over the thoracic and lumbar vertebrae, and pelvic bones muscles. This dog also is thin (i.e., low body condition score), but animals can have significant muscle loss and still be normal or overweight.

A dog with mild cardiac cachexia secondary to naturally occurring degenerative mitral valve disease and congestive heart failure. At this stage, muscle loss is only noted in the epaxial muscles over the thoracic and lumbar vertebrae. Because the dog has an ideal body condition score, the mild muscle loss can be easy to miss. Identification of cachexia in its early and more subtle stages requires awareness and careful evaluation, including palpation of the major muscle groups, and is a key to successful management.
Fig 3  Muscle loss can be readily identified clinically using a muscle condition score (MCS) chart. Assessment of muscle loss is based on visual examination and palpation of muscle mass over the head, scapulae, epaxial muscles over the thoracic and lumbar vertebrae, and pelvic bones. An MCS chart developed by Tufts University and the World Small Animal Veterinary Association [26]. This scoring system classifies dogs as having normal muscle, or mild, moderate, or severe muscle loss. There is a separate MCS chart for cats [26]. The MCS chart is provided courtesy of the World Small Animal Veterinary Association.

Muscle Condition Score

Muscle condition score is assessed by visualization and palpation of the spine, scapulae, skull, and limbs of the dog. Muscles in the limbs are particularly noted in the epaxial muscles on each side of the spine. Muscle loss at other sites can be more variable. Muscle condition scores are graded as normal, mild loss, moderate loss, or severe loss. Normal animals do not have significant muscle loss. If they are overweight (body condition score > 5), considerable muscle loss can occur (body condition score < 3). Underweight is indicated by a low body condition score (< 3). In severely underweight animals, muscle loss is more severe and is noted in the head and limbs. An example of each score is shown below.

Muscle Condition Score Chart

- Normal muscle mass
- Mild muscle loss
- Moderate muscle loss
- Severe muscle loss

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Fig 4  Transverse ultrasound images of the right epaxial muscles at the level of the 13th thoracic vertebra (T13) of a healthy young pet dog illustrating measurement of epaxial muscle height. * denotes the right transverse process of T13 and the articulation with the 13th rib. † is centered in the hypoechoic epaxial muscles. Arrowheads indicate the hyperechoic interface of the T13 lamina. The diamond is at the ventral aspect of the spinous process. The ultrasound calipers (crosses) measured a muscle height of 0.98 cm. Used with permission from the Canadian Veterinary Medical Association [29].
Specific forms of cachexia and sarcopenia

The hallmark of all forms of cachexia and sarcopenia is loss of LBM with functional deficits. However, different forms of cachexia do have some unique features which will be described in more detail for the most commonly associated diseases seen in dogs and cats.

Cardiac cachexia

Heart disease in dogs and cats

Heart disease is one of the most common diseases of pet dogs and cats, with 10-15% of all dogs and cats affected by some form of heart disease and an even higher prevalence in certain breeds. Most heart disease in dogs is adult-onset (acquired), with the majority of dogs (75-80% of all heart disease) having degenerative mitral valve disease (DMVD; similar to mitral valve prolapse but with a much more progressive nature, resulting in mitral regurgitation and, often, CHF). Degenerative mitral valve disease affects approximately 11% of the general canine population but becomes even more common with age: 30% of dogs >13 years of age have clinical evidence [30, 31]. Another 5-10% of dogs with acquired heart disease have dilated cardiomyopathy (DCM), and the remaining dogs with acquired heart disease have pericardial disease, endocarditis, primary arrhythmias, heartworm disease, and congenital heart disease [31]. Small- to medium-sized dog breeds (e.g., Cavalier King Charles Spaniels, Dachshunds, miniature Poodles) are predisposed to DMVD, while DCM is the most common cause of CHF in large- and giant-breed dogs (e.g., Doberman Pinschers, Irish Wolfhounds, Great Danes). However, there are a number of specific breed predispositions. For example, Boxers are predisposed to arrhythogenic right ventricular cardiomyopathy [32], >50% of Doberman Pinschers are affected by DCM [33], and nearly 100% of Cavalier King Charles Spaniels develop DMVD [34]. Heart disease also occurs in cats, affecting 10-15% of all pet cats [35]. The most common heart disease in cats is hypertrophic cardiomyopathy (HCM), but other cardiomyopathies and congenital diseases also occur [36]. Breed predispositions also occur in cats with Maine Coon cats, Ragdolls, and Persians being at increased risk for HCM, and myosin binding protein C mutations identified in Maine Coon and Ragdoll cats [37]. Progression of heart disease can be variable but all of the above-mentioned diseases in dogs and cats often progress to CHF. Arrhythmias and sudden death also can occur. In cats, arterial thromboembolism is an important and relatively common outcome in heart disease.

Heart disease is routinely diagnosed and monitored in dogs and cats just as it is in humans using physical examination, natriuretic peptide testing, radiography, electrocardiography, and echocardiography. Specialized cardiovascular tests, such as Holter and event monitor recorders, CT, magnetic resonance imaging, and cardiac catheterization also are performed by board-certified veterinary cardiologists at tertiary veterinary referral hospitals. Medications include most of those used in humans, including calcium channel blockers, beta blockers, angiotensin converting enzyme inhibitors, diuretics (e.g., furosemide, spironolactone), anti-thrombotics (e.g., low molecular weight heparins, clopidigrel), and antiarrhythmics. Nutritional modifications are also a mainstay of therapy for heart disease.

Although the diseases mentioned thus far are very similar to those found in people in terms of pathology, clinical signs, diagnostic testing, and treatment, one heart disease which is very different across species is atherosclerosis, which is rare in dogs and cats. This may be primarily because of dogs' and cats' naturally high HDL fractions, but this species difference is not completely understood.

Cardiac cachexia in dogs and cats

Cardiac cachexia is the form of cachexia that has been longest recognized in companion animals. Studies have shown that 48-54% of dogs with CHF have some degree of cachexia [38][Freeman, unpublished data]. Another study identified that while only 14% of dogs and 12% of cats with CHF were thin (i.e., low BCS) at the time of diagnosis, 56% of dogs and 40% of cats lost weight during the course of treatment [39, 40]. Cardiac cachexia typically is recognized only after CHF has developed, and animals with right-sided CHF have more muscle loss compared to those with left-sided CHF [38].

Cardiac cachexia in dogs is associated with alterations in hemoglobin and hematocrit, as well as CD4+ and CD8+ lymphocytes, similar to immunological changes in humans with cachexia [41]. And, while not looking specifically at muscle loss, dogs with CHF that lost weight [39] and cats with CHF that were thin [40] had significantly shorter survival times compared to those of stable or normal weight.

The negative effects of cardiac cachexia are well known. However, emerging data on obesity in heart failure also is similar to that from human CHF patients. While obesity is a risk factor for the development of heart disease in humans, obesity appears to have a protective effect once heart failure is present - this is known as the obesity paradox, with obesity and overweight being associated with lower all-cause and cardiovascular mortality compared to underweight patients [42]. Although there are a number of hypotheses, the benefit of obesity in CHF may be due more to a lack of cachexia, rather than to the obesity per se. A recent human study showed that the effects of the obesity paradox are independent of adipose tissue and more related to LBM [43]. An obesity paradox has been identified in both dogs and cats with CHF [39, 40]. In cats with CHF, cats with low body weights had shorter survival times compared to cats with moderate or high
body weights [40]. As opposed to most human studies, there was a J- or U-shaped curve, rather than a linear relationship, with cats at the lowest and highest weights having the shortest survival times.

Similar factors appear to play an important mechanistic role in canine and feline cardiac cachexia compared to humans. Tumor necrosis factor-α (TNF), for example, is elevated in both dogs and cats with CHF [38, 44]. 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 [45, 46]. As in humans with CHF, circulating insulin-like growth factor-1 (IGF-1) concentrations were shown to be an independent predictor of survival in dogs with CHF [38, 47].

Another important aspect of cardiac cachexia is reduced intake of calories and other nutrients. A complete lack of food intake (anorexia) is relatively uncommon in dogs and cats after acute CHF is controlled, but hyporexia (reduced food intake) and dysrexia (altered food preferences or eating patterns) are extremely common in dogs and cats with CHF. Our group has shown that between 34-84% of dogs and cats with heart disease have reduced food intake, which becomes more common with increasing severity of disease [14, 48, 49].

Cancer cachexia

Cancer in dogs and cats

As in humans, cancer is very common in dogs and cats. It is estimated that approximately 6 million dogs will be diagnosed with cancer each year, and nearly 20% of all pet cats will develop cancer [50]. In some breeds, the risk for cancer is particularly high. For example, in the Golden Retriever, the lifetime risk of cancer is estimated from one survey to be approximately 60%, however, a Golden Retriever Lifetime Study is currently underway to evaluate this prospectively [51]. Cancer is the cause of death in 15-27% of all dogs [52, 53], and the leading cause of death for older dogs [54]. The most common cancers in dogs and cats vary somewhat among countries, but generally include non-Hodgkin’s lymphoma, breast cancer, osteosarcoma, soft tissue sarcomas, and mast cell tumors in both species, as well as fibrosarcomas and squamous cell carcinomas in cats [55]. However, most cancers found in humans are also diagnosed in dogs or cats (e.g., melanoma; brain tumors; prostate, lung, bladder, and head and neck carcinoma). As with heart disease, there are breed predispositions: a few examples include osteosarcoma in the Irish Wolfhound, Scottish Deerhound, and Great Dane; histiocytic sarcoma in Flat-Coated Retrievers and Bernese Mountain Dogs; brain tumors in Boxers, Golden Retrievers, French Bulldogs, Boston Terriers, and Rat Terriers; and bladder cancer in the Scottish Terrier [56, 57].

The similarities between canine or feline cancers and their human counterparts are striking, including tumor genetics, histology, biological behavior, and response to treatment. Depending on the type and stage of cancer, dogs and cats with cancer can be treated with most of the same treatments used in humans, including chemotherapy, radiation therapy, immunotherapy, and molecular-targeted therapy. In fact, clinical trials in pet dogs and cats with cancer are being used to study promising drugs and other treatments for the animals themselves, as well as for humans [58]. The National Cancer Institute's Center for Cancer Research launched the Comparative Oncology Program in 2003 “to help researchers better understand the biology of cancer and to improve the assessment of novel treatments for humans by treating pet animals - primarily cats and dogs - with naturally occurring cancer, giving these animals the benefit of cutting-edge research and therapeutics” [50]. Multi-institutional clinical trials in dogs with cancer are conducted through the Comparative Oncology Trials Consortium (COTC), a network of academic comparative oncology centers managed by the Comparative Oncology Programs. The goal of this effort is to develop successful treatments for human cancer patients. In addition to clinical trials, a valuable resource for advancing the understanding of and treatment for cancer is the Canine Comparative Oncology and Genomics Consortium [59]. This group, funded by the National Cancer Institute and Pfizer, has a well-described biospecimen repository of tissues from dogs with tumors.

Cancer cachexia in dogs and cats

In humans, cancer is one of the most common diseases in which cachexia is present. In studies of pet dogs and cats with cancer, only between 4-5.5% were assessed as being thin (i.e., having a low BCS) at the time of diagnosis, with a large percentage (36-55%) being overweight [60-62]. However, this reflects the importance of looking beyond overall body condition and adipose tissue: one study reported that 69% of dogs had experienced weight loss before diagnosis (31% had <5% weight loss, 14% had lost 5-10%, and 23% had weight loss of >10%) [60]. In addition, although the prevalence of thin animals was low, 35% of dogs had mild to severe muscle loss. A study in cats with cancer identified muscle loss in 91% of affected cats [63]. Muscle loss was common (72%) even in cats that were overweight. In addition, studies in both cats and dogs have shown that thin animals had a significantly shorter survival time compared to those that were normal or overweight [62, 63]. This underscores the importance of assessing not only BCS (which assesses fat stores) but also MCS (which specifically assesses muscle) and changes in body weight in order to detect cancer cachexia.

Renal cachexia

Kidney disease in dogs and cats
Like heart disease and cancer, kidney diseases are very common in dogs and cats. The most common disease in both species is CKD, which is most often the result of tubulointerstitial nephritis or glomerulonephritis. Other diseases of the kidneys also can occur, including polycystic kidney disease (especially in certain feline breeds, such as the Persian cat), nephrolithiasis, and amyloidosis [11, 64]. The prevalence of CKD is estimated to be 0.5-1.5% of dogs and 1-3% of cats, with much higher rates in older animals [64]. In fact, one recent study reported that the prevalence of CKD was 50% among cats of all ages, but was 81% in cats ≥15 years of age [65]. Small size and some specific breeds have been associated with increased risk for CKD [64]. Especially in cats, CKD is a common cause of death, with one study reporting that kidney disease was the most common cause of death for cats > 5 years of age [66].

Renal cachexia in dogs and cats

Although the prevalence of cachexia in dogs and cats with CKD has not specifically been measured, studies noting body condition of cats with CKD have reported that 36-66% of cats with CKD are thin and 42-82% have lost weight [67-72]. Cats with CKD that are thin have a shorter survival time compared to cats that are normal or overweight [72, 73]. Similar to cats with CHF, there appears to be an obesity paradox for cats with CKD, with a U-shaped curve: the lowest survival is for cats with a low body weight, followed by cats that are very overweight, with cats in the middle weight having the longest survival times (Fig 5) [72]. The obesity paradox also appears to exist in dogs with CKD, as it does in humans with CKD [74, 75], with thin dogs having significantly shorter survival times compared to normal weight or even overweight dogs [76].

The mechanisms of renal cachexia in dogs and cats have not been fully examined but changes in food intake are an important contributing factor. Studies have shown that the prevalence of reduced food intake in cats with CKD ranges from 21-92% [67-69, 70, 71, 73, 77].

Other forms of cachexia

Other common diseases affecting pet dogs and cats are associated with weight and muscle loss (e.g., chronic respiratory diseases, hepatic disease, diabetes mellitus, trauma, critical illness). However, the prevalence and outcomes of cachexia in these diseases has not been as well documented.

Sarcopenia

Pets are living longer and, like humans, dogs and cats lose LBM during aging [22, 78-81]. One study of laboratory dogs reported an age-related decline in total body protein, as well as higher mean body fat in geriatric dogs compared to younger dogs [78]. Two studies of healthy Labrador retriever dogs in research colonies found a significant loss of LBM (using DEXA) during aging [80, 81]. Similarly, in a study of healthy young (1-5 years) and geriatric (>8 years) pet Labrador retriever dogs, the mean epaxial muscle area measured by ultrasound and CT was significantly lower in healthy geriatric dogs compared with healthy young dogs (Fig 6) [22]. There is less information from cats, but one study measured muscle by DEXA and MCS in cats in a colony ranging in age from <6 months to >10 years of age. Investigators identified a significant negative correlation between MCS and age (r = -0.75, p<0.001) [25].
Fig 5  Hazard ratio based on body weight at the time of diagnosis of chronic kidney disease (CKD) in 569 cats. Dotted lines indicate the 95% confidence interval. Cats with the lowest and highest body weights at the time of diagnosis of CKD had shorter survival times than cats with more moderate body weights (P < .0001). This figure was originally published in an open access journal [72], and is available under the terms of the Creative Commons Attribution Non-Commercial License CC BY-NC which permits non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited.

Fig 6  Transverse computed tomography image of the epaxial musculature at the level of T13 from a young (4-year-old) spayed female Labrador Retriever. Notice the contrast between bone, muscle, and fat. The left epaxial musculature area (asterisk inside area indicated with a white line) has been measured with a closed polygon tool and determined to be 9.38 cm². Used with permission from the American Veterinary Medical Association [22].
Mechanisms and potential interventions in dogs and cats

Recent basic science studies and human clinical trials are shedding light on the mechanisms and pathways of cachexia and sarcopenia. There are exciting opportunities for new and effective targets to enhance food intake, improve nutrient absorption, and modify metabolic and inflammatory pathways to prevent, ameliorate, and even reverse, the effects of cachexia and sarcopenia. Medications being investigated for the treatment of cachexia and sarcopenia in humans have been previously reviewed [82-85], so they will not be reviewed here. Instead, the focus will be on where these treatments have been studied in companion animals. At this time, few of these interventions have been studied in companion animals, but the burgeoning interest in these syndromes in humans is likely to result in the development of products that may have benefits through off-label use in animals or may spur interest in the veterinary pharmaceutical industry. However, companion animals also provide a naturally-occurring large animal model of cachexia and sarcopenia in which promising treatments can be tested before (or in parallel to) human clinical trials. Effective pharmacologic treatments not only need to increase body weight, but need to increase LBM and improve muscle function.

Myostatin

Myostatin negatively regulates skeletal muscle mass and myostatin mutations result in enlarged musculature [86-91]. These changes may be desirable in food-producing animals, such as cattle (double muscled cattle breeds, such as the Belgian Blue and Piedmontese)[86-88] or sheep (Texel sheep) [89], or even in companion animals where "bully" whippets have increased racing speed [91]. However, if myostatin levels are elevated, which occurs in both animal models and humans with CHF [92, 93], muscle loss occurs. Conversely, blocking myostatin may be beneficial in cachexia and sarcopenia by increasing muscle mass. A number of promising studies in rodent models of cachexia have been completed [7], and several Phase 1 and 2 human clinical trials are underway to study the effects of myostatin inhibitors in muscular dystrophy, cancer, and kidney disease (www.clinicaltrials.gov). A small, open-label pilot study of a myostatin antagonist (activin receptor type IIB) was conducted in pet dogs with naturally-occurring CHF [94]. While no significant improvements occurred in body weight, there was a numerical, but not significant, increase in MCS.

Ghrelin

Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor that is secreted in response to fasting and results in increased food intake. However, ghrelin also has a effects throughout the body. Ghrelin modulates growth hormone secretion (and thus, IGF-1 production), and can have beneficial effects on muscle mass, inflammation, cardiac function, gastric motility, and many others [95]. Ghrelin concentrations are increased in people with CHF but food intake is decreased, suggesting loss of normal feedback and resistance to ghrelin [96-99]. However, ghrelin administration appears to overcome ghrelin resistance and results in weight gain in rodent models of CHF [100-102], and improved cardiac function, LBM, and muscle strength in one open-label study in humans [103]. A variety of ghrelin agonists have been developed, including ghrelin receptor agonists. One well-studied ghrelin receptor agonist is anamorelin, which has been studied in multiple human clinical trials, including 2 large phase III clinical trials in patients with non-small cell lung cancer (ROMANA 1 and 2 studies) [104]. In those studies, anamorelin significantly increased LBM, but did not significantly increase handgrip strength [104]. In a safety extension study (ROMANA 3), anamorelin remained well-tolerated and also improved symptom burden [105].

Capromorelin, ghrelin receptor agonist that is related to anamorelin, was recently approved by the FDA as an appetite stimulant for dogs, and is being tested in cats as well. It was shown in laboratory studies in healthy Beagles to be safe and effective at increasing food intake and body weight, as well as increasing growth hormone and IGF-1 [106-109]. In a clinical trial in dogs with reduced appetite, the drug was shown to increase appetite and body weight [110]. While it is labeled for appetite stimulation, the beneficial effects of ghrelin on LBM and other organs make it a promising drug for cachexia and sarcopenia. Capromorelin has been studied in laboratory cats, and was shown to be safe and effective at increasing food intake and body weight [111, 112].

Omega-3 fatty acids

Increased dietary long-chain polyunsaturated omega-3 fatty acids, either from a highly enriched diet or through supplements, have a number of benefits in animals with cachexia or sarcopenia. Omega-3 fatty acids reduce the more inflammatory eicosanoids and decrease TNF and interleukin-1 production. One study showed that dogs with CHF have significantly lower omega-3 fatty acid concentrations compared to healthy controls, and that omega-3 fatty acid supplementation increased concentrations [38]. Omega-3 fatty acids have been shown to decrease the muscle loss in dogs with CHF and, in some animals, to improve appetite [38]. These results are similar to studies in humans in which omega-3 fatty acids increased body weight in patients with CHF [113] and increased muscle mass in elderly men [114]. Omega-3 fatty acids have antiarrhythmic effects and also may enhance myocardial energy metabolism [115, 116]. One retrospective study in dogs with naturally-occurring CHF identified an association between omega-3 fatty acid administration and longer survival time [39].
Studies of omega-3 fatty acids in other forms of cachexia in dogs and cats have had less promising results. Two studies in dogs with lymphoma failed to show a benefit of a diet highly enriched in omega-3 fatty acids on body weight, survival, or quality of life [117, 118]. In kidney disease, some studies of omega-3 fatty acids in dogs and cats have shown beneficial effects [119-121].

The optimal dosage of omega-3 fatty acids for different diseases and stages of disease has not been determined, but recommendations have been made using the best available evidence [116, 122]. The recommended dosage of fish oil for dogs and cats (e.g., 40 mg/kg eicosapentaenoic acid and 25 mg/kg docosahexaenoic acid for animals with CHF) is higher than that which is typically used in humans. This dose typically requires supplementation although a few specially designed canine and feline therapeutic diets contain high enough levels of fish oil to achieve the recommended dose from diet alone. There are some notable species differences in fatty acid metabolism that are important to consider. Flax seed oil and other plant-based omega-3 fatty acids are inefficient (dogs) or ineffective (cats) sources of omega-3 fatty acids because of reduced or very low hepatic elongation of α-linolenic acid to EPA and DHA in dogs and cats, respectively [122].

**Nutrition**

In addition to medication targeting various mediators or pathways involved in cachexia and sarcopenia, nutrition also plays a critical role in treating these conditions [123]. To be most effective, treatment for cachexia should be multimodal and include an anti-inflammatory effect to decrease muscle loss (e.g., anti-inflammatory agents) and an anabolic effect to enhance protein synthesis (e.g., resistance exercise), but also requires adequate substrate (i.e., calories, protein, and other nutrients) [124]. These are above and beyond optimal treatment for the underlying disease. For example, treatments targeting anabolism cannot be fully effective if there is insufficient substrate. In the treatment of cachexia and sarcopenia, optimal nutrition, whether for humans or companion animals, can be challenging because of underlying diseases (e.g., renal, cardiac or hepatic failure; cancer; respiratory disease), but is critical for successful outcomes so should be an integral part of research and clinical practice. In dogs and cats, a wide variety of therapeutic diets are available to optimize nutritional profiles and food intake, and nutritional support techniques (e.g., feeding tubes, parenteral nutrition) are used to help improve food intake and quality of life for these patients.

**Advantages of companion animals as models for cachexia and sarcopenia**

Although companion animals can provide an important stepping stone between basic research or rodent models and human clinical trials, it is important to incorporate these natural large animal models appropriately. There are advantages and disadvantages to these naturally-occurring animal models (Table 1). Veterinarians can help physicians and other scientists to determine the most appropriate species and breed, and if studying animals in a colony or conducting clinical trials in pets is better suited for the research question and outcomes of interest. For example, animal colonies can be genetically-defined, whereas pets are not typically screened for gene mutations (although this can be done for some mutations, such as those involved in certain cardiomyopathies). Just as in human clinical trials, invasive procedures cannot be performed in clinical trials involving pets, although can be included in studies using large animal models in laboratories (with proper animal welfare considerations and approvals). There are limitations in species-specific antibodies and commercial immunoassays, compared to the wide array available for humans and rodent models. However, this also provides ample opportunities for biotech companies. Some specific opportunities to collaborate or learn more about cachexia and sarcopenia in companion animals are listed below:

- Learn about current clinical trials in companion animals. Animal clinical trials can be shorter and less expensive since dogs and cats often reach endpoints (e.g., heart failure, cachexia, death) earlier than humans. There are numerous, ongoing clinical trials in a variety of naturally-occurring diseases in companion animals, including those that are associated with cachexia. Clinical trials in companion animals must undergo approval (by an Institutional Animal Care and Use Committee or similar body) and pet owners must sign an informed consent form before volunteering to enroll their pets, along with a number of other safeguards for both the pet owner and the pet. A list of some of the current clinical trials across the United States can be found in the American Veterinary Medical Association’s Clinical Trials Registry (https://ebusiness.avma.org/aahsd/study_search.asp) and on individual veterinary school website’s (e.g., http://sites.tufts.edu/vetclinicaltrials).

- Read about published research using naturally-occurring animal models of cachexia and sarcopenia. Most veterinary studies are indexed in Medline and can be accessed via Pubmed or Ovid. However, some veterinary studies are indexed only in CAB Abstracts. Therefore, one must deliberately seek out studies using naturally-occurring animal models.

- Invite veterinarians to give sessions at specialty meetings (e.g., cardiology, oncology). The interactions can be beneficial from both a clinical and research perspective.

- Collaborate with veterinarians and veterinary specialists in research. Despite the many similarities between human and companion animal diseases, there are some important metabolic, nutritional, and anatomic differences across species that are...
important to consider to optimize study design. An interdisciplinary approach provides important advantages for optimal study design and in grant applications.

- Reach out to a veterinary specialist to learn more. There are more than 20 veterinary specialties, including oncology, neurology, cardiology, internal medicine, critical care, and nutrition. These veterinary specialists are located at all 30 veterinary schools in the United States (and in most veterinary schools throughout the world) and their numbers in private specialty practices are increasing as well. Listings of board-certified veterinary cardiologists, oncologists, internists, neurologists, and surgeons can be found online (http://find.vetspecialists.com). Links to other specialties can be found on the American Board of Veterinary Specialties website: https://www.avma.org/ProfessionalDevelopment/Education/Specialties/pages/recognized-veterinary-specialty-organizations.aspx

**Table 1: Advantages and disadvantages of studying companion animals as naturally-occurring models of cachexia and sarcopenia**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>More representative of human disease than rodents than rodents</td>
<td>Cost (laboratory studies are more expensive</td>
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<tr>
<td>Compressed progression of disease trials</td>
<td>Invasive tests/samples not possible in clinical</td>
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<tr>
<td>Short gestation time and lifespan</td>
<td>Ethical concerns (laboratory studies)</td>
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<tr>
<td>Genome sequenced</td>
<td>Species-specific antibodies/molecules not</td>
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<td>always available</td>
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<tr>
<td>Larger size than rodents</td>
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<tr>
<td>Cost (clinical trials less expensive than humans)</td>
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<tr>
<td>Genetic diversity (clinical trials)</td>
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<tr>
<td>Breed predispositions</td>
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<tr>
<td>Similar environmental exposures to humans (clinical trials)</td>
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<tr>
<td>Diet can be controlled (clinical trials and laboratory studies)</td>
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<tr>
<td>Diseases associated with cachexia are common</td>
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**Conclusions**

Improved treatments for sarcopenia and cachexia are critical to optimize patient care, whether for humans or companion animals. The aging pet population; increased diagnosis of diseases such as CHF, cancer, and CKD; and an increasing willingness of pet 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 humans. Science often approaches challenges from traditional siloes of individual disciplines, rather than using an interdisciplinary and collaborative approach that could accelerate translation of research into effective treatments. However, studying dogs and cats with naturally-occurring cachexia and sarcopenia - either as clinical trials in pets or research in genetically-defined colonies - could provide an important stepping stone between basic science research and human clinical trials. At the same time, discoveries in humans can spur advances in the treatment of dogs and cats with these conditions.

**Conflict of Interest Disclosure**

Dr. Freeman has received consulting fees and speaking honoraria and serves on a scientific advisory council for Aratana Therapeutics.

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