



Muscle Matters in the Geriatric CKD Pet: Working Against the Clock

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In 2010, 8% of the world's human population was 65 years of age or older. By 2050 this number is expected to triple to 16% of the world's population.¹ With the growing human geriatric population has come increasing interest in diseases commonly afflicting geriatric patients as well as unavoidable age-related syndromes impacting quality of life and ability to live independently. Like humans, pets are also aging and there is increased interest in how to improve their quality and quantity of life. One syndrome speculated to affect all aging individuals (human, canine and otherwise) is sarcopenia, the age-related loss of lean body mass (LBM) in the absence of disease. Sarcopenia encompasses both a loss of muscle mass and function. Furthermore, many geriatrics also suffer from chronic diseases such as chronic kidney disease (CKD) which occurs in 32% of cats 15 years of age or older.² Such diseases also impact LBM through mechanisms involved in cachexia, which is muscle loss due to disease. Together, sarcopenia

and cachexia represent important syndromes impacting quality and quantity of life in much of our geriatric population.

Importance

Sarcopenia occurs in all aging individuals. In humans, there is loss of 5% of muscle mass per decade of life from the fourth decade onwards, potentially increasing after the age of 65 years.³ The rate of muscle loss in aging pets has yet to be investigated but is likely much higher due to their relatively shorter lifespans. Sarcopenia is a newly emerging area of interest in veterinary medicine; however, it is a topic of extensive research within the human medical field due to impact on quality of life, as well as its direct association with morbidity and ability to live independently. Similarly, the veterinary profession has begun to consider the effect of age-related muscle loss on the quality of life in our patients. This is particularly of interest in pets already suffering from muscle loss due to chronic disease

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such as CKD or congestive heart failure (CHF). Many of these pets have lost significant LBM, impacting their mobility, quality of life, and likely mortality: in humans suffering from disease it has been demonstrated that cachexia is an independent predictor of mortality.⁴ While yet to be investigated it is likely that cachexia indirectly impacts survival time in pets. Cachexia results in several negative outcomes associated with quality of life, which play a pivotal role in clients' choice of euthanasia. Addressing causes of muscle loss in aging, diseased patients is therefore of great interest. This has led to the creation of muscle condition scoring (MCS) systems for dogs and cats (such as those found in the World Small Animal Veterinary Association Nutrition Toolkit (<http://www.wsava.org/nutrition-toolkit>) designed for use in medical records and pilot studies to document the existence of sarcopenia and cachexia in veterinary patients. In order to understand how to manage these syndromes, it is important to first grasp the pathophysiologic mechanisms involved.

Mechanisms

Sarcopenia and cachexia are both multifactorial syndromes and the underlying mechanisms involved in each overlap considerably (Figure 1). Muscle mass results from the balance between anabolic and catabolic pathways involved in protein synthesis or breakdown respectively. Both pathways are impacted negatively in cachectic and sarcopenic individuals. Aging as well as chronic disease may result in decreased concentrations, and/or signaling of hormones critical to protein synthesis including insulin-like

growth factor-1 (IGF-1) and growth hormone (GH) as well as insulin-resistance. Cachectic individuals also have increased concentrations of cortisol and adrenergic hormones resulting in increased fat oxidation, insulin-resistance and hypermetabolism.⁵ Inflammatory mediators (e.g., interleukin (IL) -1 β , 6, and tumor necrosis factor alpha (TNF- α) through activation of the ubiquitin-proteasome pathway via NF- κ B-dependent and independent mechanisms) are increased in cachectic individuals and contribute to decreased food intake and protein catabolism. These cytokines also contribute to insulin-resistance as well as other mechanisms that impact protein synthesis such as inhibition of GH and IGF-1. An observational study in more than 2,000 men and women showed an association between TNF- α and decline in muscle mass and strength.⁶

Mitochondrial efficiency is also compromised with age and disease

lower activity of antioxidant enzymes including superoxide dismutase and glutathione peroxidase as well as inhibition of protein synthesis.⁷ Similar mechanisms related to oxidative stress are likely involved in degenerative age-related conditions including sarcopenia as expressed in the Free Radical Theory on Aging (also known as the Oxidative Stress Theory of Aging).

The role of myostatin, a member of the transforming growth factor-beta (TGF- α) superfamily responsible for controlling growth of muscle, is still unclear. While some studies have documented benefits of myostatin inhibitors in human cancer patients with cachexia, other studies have reported negative results. As outlined above, many factors involved in cachexia and sarcopenia have been identified in humans and further research is needed to understand any differences that may exist in mechanisms involved in muscle loss in dogs and cats.

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and is thought to contribute to decreased muscle mass through a number of mechanisms. Oxidative stress has been well documented in humans suffering from chronic disease and is believed to play an important role in protein catabolism. In part this may result from stimulation of the ubiquitin-proteasome system and

Management

While there is no single therapy available that will halt cachexia or sarcopenia, a multimodal approach, including pharmacologic and nutritional intervention in addition to exercise programs, may minimize muscle loss due to these syndromes. And in the case of cachexia,

addressing the underlying disease is imperative for minimizing loss of LBM.

Several novel pharmacologic therapies are currently undergoing trials for use in both cachectic and sarcopenic humans and may serve as a starting point for therapeutic opportunities that may benefit veterinary patients in the future. For example, one intervention undergoing extensive study is recombinant GH, which has been shown to increase LBM in healthy geriatric men and is currently being used to manage cachexia in a number of chronic diseases in humans. GH acts primarily through IGF-1 as a powerful stimulus of muscle synthesis but supplementation is not without side effects. Ghrelin mimics (also known as GH secretagogues) enhance appetite and their use in patients with cachexia and sarcopenia is an area of active research. Studies investigating ghrelin mimics have demonstrated improved appetite, GH secretion, and increased body weight and LBM in aging humans.^{8,9} The first ghrelin mimetic for veterinary use will be commercially available in 2017; its benefits beyond appetite stimulation in pets with muscle wasting are yet to be seen. Many other novel pharmacologic agents such as anti-IL-6 antibodies and myostatin inhibitors are being investigated for management of sarcopenia and cachexia but are beyond the scope of this review.

In humans, both resistance and aerobic exercise have been shown to be effective in minimizing muscle loss and improving muscle function, as well as attenuating inflammatory markers, reducing fatigue, and improving quality of life in geriatric

and cachectic patients suffering from loss of LBM.¹⁰ These actions are thought to be due to anabolic effects of exercise including stimulation of IGF-1, inhibition of inflammatory mediators and myostatin, as well as increased antioxidant capacity through enhancement of free radical scavenging enzymes and other mechanisms. While instituting such programs poses unique challenges in veterinary patients, it is possible and likely would be enjoyed by the majority of canine patients. Simple plans could include increasing normal daily activities of a geriatric canine patient (short walks, hikes, and playing catch) and may improve their agility and attenuate muscle loss. Cats can often be encouraged to exercise through play activities such as replicating the hunt experience, utilizing stairs and laser pointers. Many geriatric dogs and cats suffer from degenerative joint disease (DJD), which may impact their level of activity; this can be effectively managed through nutritional interventions (therapeutic joint diets, omega-3 [n-3] fatty acid supplementation) as well as judicious pharmacologic pain management. Addressing DJD often greatly enhances self-initiated exercise in geriatric dogs and cats and may assist in improving quality of life, mobility, and muscle mass/function with little cost or risk to the family. It is critical that the veterinary team addresses such conditions when instituting plans to increase a geriatric patient's activity.

Nutrition holds great potential for combating many of the mechanisms involved in both cachexia and sarcopenia. Inflammation is believed

to play a fundamental role in development of age- and disease-related muscle loss as outlined above. Long-chain n-3 fatty acids have demonstrated anti-inflammatory effects in both humans and dogs and cats and therefore may assist in attenuating the inflammatory component that is so fundamental in both of these syndromes. On the veterinary side, n-3 fatty acids have also been shown to improve appetite and reduce muscle loss in dogs with heart failure.¹¹

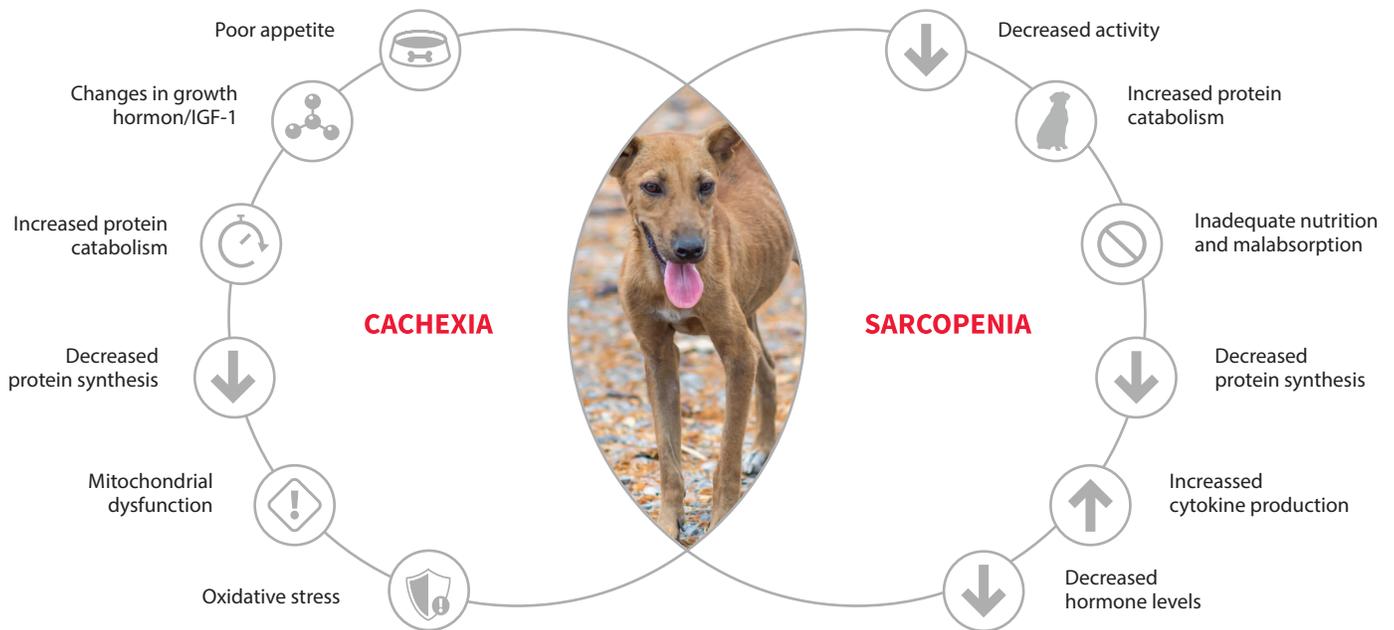
Antioxidants and mitochondrial cofactors may also be beneficial as part of multimodal therapy for muscle wasting syndromes, due to the pivotal role that oxidative stress plays in their pathogenesis. One recent phase III study in humans found significant improvements in cancer patients' LBM, resting energy expenditure and fatigue when a combination regimen of antioxidants, anti-inflammatory, and pharmacologic agents (eicosapenoic acid, megestrol acetate, carnitine, and other agents) were given compared with any of the interventions given alone.¹² While efficacy of antioxidants appears promising for patients with cachexia, optimal dosage, route of administration, or the most effective combinations have not been established, and studies in veterinary patients at this time are lacking.

In veterinary patients suffering from muscle loss it is also critical that caloric and protein requirements are met daily. This is an issue plaguing CKD patients. While renal therapeutic foods have historically been characterized as unpalatable, recent studies found that 94% of cats

and 97% of dogs with CKD successfully transitioned to Hill's® Prescription Diet® k/d®.^{13,14} Nonetheless, hyporexia (decreased food intake) is quite common in the CKD patient. In the case of insufficient caloric intake, muscle will ultimately be catabolized to provide a necessary source of energy. Patients eating insufficient calories are often also not meeting their protein requirements, further perpetuating muscle loss. While

studies focused on supplementing protein or specific amino acids in humans have shown mixed benefits, it is generally agreed that meeting the patient's basic need for nitrogen and the essential amino acids is imperative. Since insufficient caloric and protein intake further exacerbates muscle wasting in cachectic pets, it must be prevented when possible through meticulous use of antiemetics, appetite stimulants,

proper feeding orders, and when necessary and appropriate, enteral nutritional interventions such as esophagostomy tube placement. A thorough nutritional assessment as part of every patient visit greatly reduces the risk of malnutrition in both healthy and diseased senior pets.



▲ **FIGURE 1** Overlapping Mechanisms of Cachexia and Sarcopenia

TABLE

NON-PHARMACOLOGIC MULTIMODAL MANAGEMENT OF CACHEXIA AND SARCOPENIA

Minimize Muscle Loss

- ▶ Maximize treatment of underlying conditions
- ▶ Omega-3 fatty acids from fish oil
- ▶ Targeted levels of L-carnitine

Meet Nutrient Needs

- ▶ Ensure caloric needs are met daily
- ▶ Meet essential amino acid needs
- ▶ Consider anti-emetics, appetite stimulants
- ▶ Consider feeding tubes in consistently anorexic patients

Maximize Muscle Synthesis

- ▶ Maximize quality of life to keep pets moving
- ▶ Targeted levels of L-carnitine

While there is no single therapy shown to mitigate muscle loss associated with aging and disease, a multimodal approach including nutritional and exercise therapies can provide meaningful benefits that improve quantity and quality of life in our

aging, diseased patients. The human medical community has made great strides towards better understanding and slowing of these clinically important syndromes. Veterinarians are charged with following this exploration into these critical,

devastating syndromes and have taken the first steps through creation of muscle condition scoring systems and pilot studies documenting that such syndromes indeed exist in our patient population.

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