

Cachexia, Sarcopenia and Other Forms of Muscle Wasting: Common Problems of Senior and Geriatric Cats and of Cats with Endocrine Disease

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Abstract

Cachexia and sarcopenia are two important syndromes associated with muscle wasting that occur in acute and chronic disease and in aging, respectively. Our studies show that old cats, like dogs and humans, also develop muscle wasting due to sarcopenia, cachexia and metabolic diseases such as hyperthyroidism and diabetes.

Of 255 clinically normal older cats evaluated, 38% had evidence of muscle wasting, with a progressive rise in prevalence as the cats' life stage advanced from mature to senior and geriatric. An even higher prevalence of muscle wasting (>75%) occurs in cats with chronic kidney disease and hyperthyroidism. More nutritional research is needed to help prevent and treat these common muscle-wasting syndromes of senior and geriatric cats.

Introduction

Cachexia and sarcopenia are two important syndromes associated with muscle wasting that occur in acute and chronic disease and in aging, respectively.^{1,2} Cachexia is a common finding in sick patients (humans, cats and dogs) characterized clinically by weight loss and muscle wasting and is associated with increased morbidity and mortality.^{1,4} Sarcopenia is similar to cachexia in that it is characterized by a loss of muscle mass, but sarcopenia occurs in the absence of disease as part of the aging process.^{1,2,4,5}

In addition to these two distinct syndromes, there are a variety of other causes for muscle wasting that do not neatly fit within the definitions for either cachexia or sarcopenia — such as muscle loss secondary to thyrotoxicosis.⁶⁻⁹ Because of this, some experts^{10,11} have proposed the more general and simple term of “muscle wasting disease” to incorporate all of these diseases or syndromes that result in a loss of muscle mass, as it is universally applicable and easily understood by the scientific community as well as the lay public.

Glossary of Abbreviations

BCS: Body Condition Score
CKD: Chronic Kidney Disease
DEXA: Dual-Energy X-Ray Absorptiometry
GH: Growth Hormone
GHS: Growth Hormone Secretagogues
IGF-1: Insulin-Like Growth Factor
ME: Metabolizable Energy
MSC: Muscle Condition Score

The prevalence of muscle-wasting disease is increasing both in human and veterinary medicine, in part because of the recognition of these syndromes. Because of the high prevalence and deleterious effects of muscle wasting, a better understanding of these syndromes is critical to optimize feline (and human) care. There is great interest in the development of dietary therapy, new drugs

and other treatments to combat these syndromes in people, as well as in cats and other companion animals.

Cachexia

Cachexia is a complicated metabolic syndrome related to underlying illness. It is characterized by loss of muscle mass — with or without the loss of fat mass — that is associated with anorexia, an inflammatory process, insulin resistance, and increased protein turnover.^{12,13}

The syndrome of cachexia has been known for centuries. Referring to people with congestive heart failure, Hippocrates wrote that “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 ... The illness is fatal.”¹⁴ The term cachexia has Greek roots, a combination of the words kakós (bad) and hexis (condition or appearance). Clinically, this muscle and fat wasting leads to poorer outcomes and is associated with a high mortality risk.¹⁵

In human patients, cachexia can develop in a variety of acute and chronic diseases, including heart failure (cardiac cachexia), cancer (cancer cachexia), chronic kidney disease (renal cachexia), and chronic obstructive pulmonary disease, as well as in patients with a variety of acute illnesses and injuries.^{3,16-20} The syndrome of cachexia also appears common in cats (and dogs) with the same medical conditions.^{16,21-23}

To our knowledge, an estimation of lean body mass loss as documented by muscle condition score or more specific measures of body composition has not been reported in

cats with acute or chronic diseases. However, our preliminary survey of 20 cats with chronic kidney disease (CKD, IRIS stage 2 to 3) showed that all of these cats had some degree of muscle wasting, with 18 cats (90%) having moderate-to-severe wasting. This muscle wasting of CKD-related cachexia is important since it can negatively impact survival time, at least in human patients with CKD.²⁴

Factors that contribute to cachexia include anorexia and a number of associated metabolic alterations, including increased inflammatory status and increased muscle proteolysis. The weight loss associated with cachexia differs from that seen in a healthy person (or cat) who loses weight. In a healthy individual who is receiving insufficient calories to meet daily requirements, metabolic adaptations allow fat to be used as the primary fuel source, thus preserving lean body mass as much as possible. In contrast, the primary fuel source in patients with acute or chronic illness is amino acids; therefore, these patients catabolize muscle (lean body mass) and waste muscle.^{3,16} Therefore, loss of lean body mass is a hallmark of cachexia, and fat is lost to a lesser degree. The loss of lean body mass has direct and deleterious effects on strength, immune function and survival.^{3,16}

Total weight loss is an insensitive measure of muscle loss, so using weight loss as the sole diagnostic criteria reduces one's ability to identify cachexia until its more advanced stages. In addition, there are certain types of cachexia (cardiac cachexia with pleural effusion) in which weight loss is masked by the accumulation of fluid. Another reason for using factors other than total weight loss for a diagnosis of cachexia is that this is a gradual process. Loss of lean body mass generally develops before marked weight loss can be detected.

Therefore, we should use clinical techniques to identify lean body mass loss at an early stage, if possible, at a time when treatments are much more likely to be successful. The muscle condition score (MCS) should be evaluated in every cat at every visit, in addition to the body weight, body condition score (BCS) and diet history (see below).^{25,26}

Sarcopenia

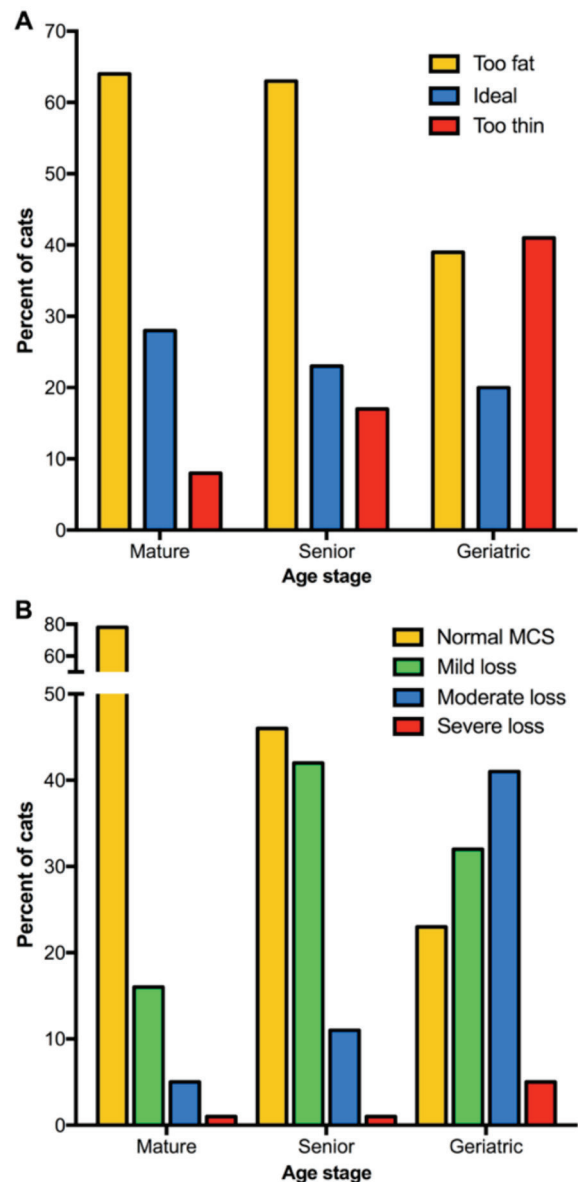
Significant loss of lean body mass can develop with aging. This loss of lean body mass — termed sarcopenia — occurs in the absence of disease, though cachexia and sarcopenia can occur concomitantly.^{1,2,17,27-29} In contrast to cachexia, which has been known for centuries, the term sarcopenia (from the Greek “sarx” or flesh plus “penia” or loss) was only first proposed in 1989 to describe this age-related loss of muscle mass and strength.³⁰

In people, sarcopenia actually begins early in life, with a 30% reduction in muscle mass from 30 to 80 years of age. In sarcopenia, loss of lean body mass often is generally accompanied by an increase in fat mass, then referred to as sarcopenic obesity,^{31,32} so the total weight may not change or may even increase, thus masking the sarcopenia. Like cachexia, sarcopenia has important clinical implications

because it is associated with physical disability, poor quality of life and increased risk of death.³³

Few studies investigating sarcopenia have been conducted in client-owned cats, but available information shows that cats also lose lean body mass during aging.^{22,34-36} In our survey of 255 cats older than 7 years of age that presented for a routine wellness examination, 96 (37.6%) cats had evidence of muscle wasting (Figure 1). As cats aged, the

Figure 1. (A) Bar graphs depicting the body condition score (BCS) of 255 clinically normal cats categorized into three groups based on their life stage (mature, senior or geriatric). As the life stage of the cats increases from mature to geriatric, notice that the prevalence of fat cats decreases while the prevalence of thin cats increases ($P < 0.0001$). (B) Bar graphs depicting the muscle condition score (MCS) of 255 clinically normal cats categorized into three groups based on their life stage (mature, senior or geriatric). As the life stage of the cats increases from mature to geriatric, notice that the prevalence of normal muscle mass decreases while the prevalence of moderate and severe muscle wasting increases ($P < 0.0001$).



prevalence of muscle wasting progressively increased, rising from 22% of mature cats (7 to 10 years) to 54% of senior cats (11 to 14 years) and up to 77% of geriatric cats (≥ 15 years). In addition, a progressive rise in the prevalence of moderate and severe muscle wasting was noted in the cats as they aged (Figure 1A). As the cats aged and lost muscle mass, a progressive rise in the number of underweight cats also was observed (Figure 1B), in accord with previously reported studies.^{22,34-36}

Metabolic Causes for Muscle Wasting

In addition to cachexia and sarcopenia, muscle wasting can develop as a result of hypermetabolic endocrine disease. In cats, common metabolic causes for muscle wasting include hyperthyroidism and diabetes mellitus, the two most common endocrine diseases of the cat.^{6,8,9,37} Since many of these hyperthyroid and diabetic cats are older, sarcopenia also likely plays a role in the loss of muscle mass in these cats.

Weight loss despite an increased appetite is the classic and most common sign seen in cats with hyperthyroidism. These cats lose weight because hyperthyroidism accelerates their metabolic rate such that energy demand exceeds energy consumption. It is important to realize that hyperthyroidism is a catabolic state.³⁸ The progressive weight loss and muscle wasting that is characteristic of feline hyperthyroid disease is caused by increased protein catabolism leading to a negative nitrogen balance.^{7,39,40}

When hyperthyroid cats first lose weight, the disorder usually can be noticed as a loss of muscle mass in the cat's lumbar paravertebral area. Despite this loss of muscle mass, most mildly hyperthyroid cats retain their abdominal adipose tissue during the initial stages of their thyroid disease and may even have a higher than ideal BCS.⁹ With time, severe muscle wasting, emaciation, cachexia, and death from starvation can occur if the cat's hyperthyroidism is left untreated.

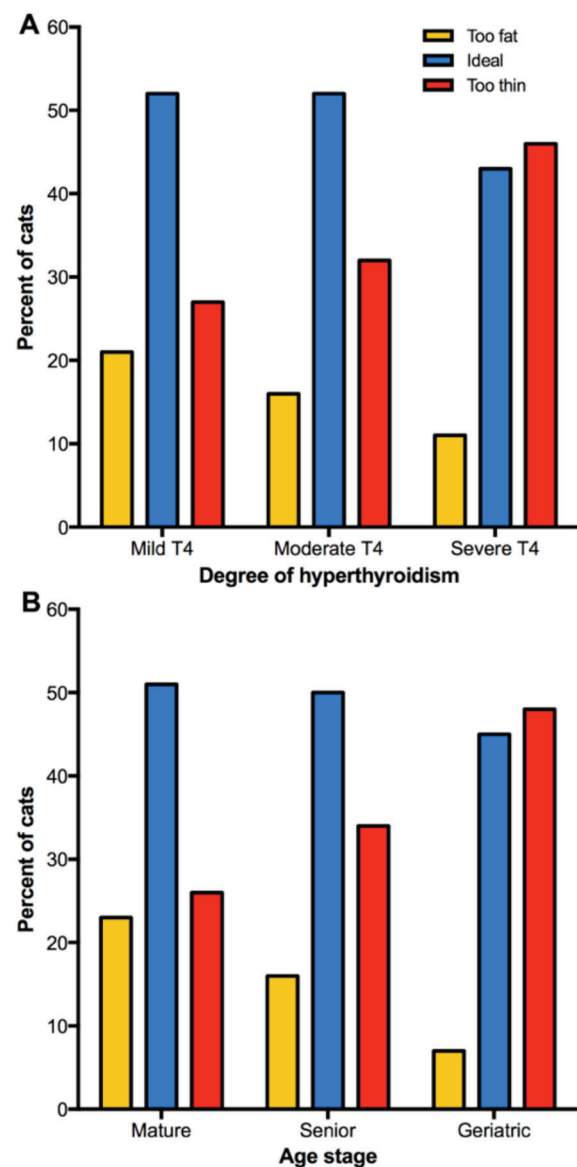
In our study of 462 untreated hyperthyroid cats, the cats' median body weight (4.36 kg) was lower than the premorbid weight (5.45 kg) recorded one to two years before diagnosis. Of the 462 cats, 35% of cats were thin or emaciated, but many more (77.3%) had loss of muscle mass. In these hyperthyroid cats, both increasing disease severity and age were associated with a lower body weight (Figure 2), as well as a higher prevalence of low BCS (thinness) and low MCS (muscle wasting) (Figure 3). In other words, severe hyperthyroidism and geriatric age both appear to contribute independently to an increased prevalence of low BCS and MCS in these cats.

After successful treatment of the hyperthyroidism with radioiodine, cats showed increases in body weight, BCS and MCS ($P < 0.001$). However, mild-to-moderate muscle wasting persisted in 45% of treated cats (Figure 4).

In summary, most hyperthyroid cats lose body weight but maintain an ideal or overweight BCS, with only one-third being underweight. As in human hyperthyroid patients, this weight loss is associated with muscle wasting, affecting >75%

Figure 2.* (A) Bar graphs depicting the body condition score (BCS) of 462 untreated hyperthyroid cats categorized into three equal-sized groups (n=154) of disease severity based on total T4 concentration (i.e., mild, moderate and severe disease). In each of the three groups, the percentage of hyperthyroid cats with low (too thin), ideal and high (too fat) BCS is depicted. As the severity of hyperthyroid disease increases, notice that the prevalence of too fat and ideal cats decreases while the prevalence of thin cats increases ($P=0.008$). (B) Bar graphs depicting the BCS of 462 untreated hyperthyroid cats categorized into three groups based on their life stage (mature, senior or geriatric). As the life stage of the cats increases from mature to geriatric, notice that the prevalence of fat cats decreases while the prevalence of thin cats increases ($P=0.0087$).

*Peterson ME, Castellano CA, Rishniw M. Evaluation of Body Weight, Body Condition, and Muscle Condition in Cats with Hyperthyroidism. *J Vet Intern Med.* 2016;30:1780-1789.

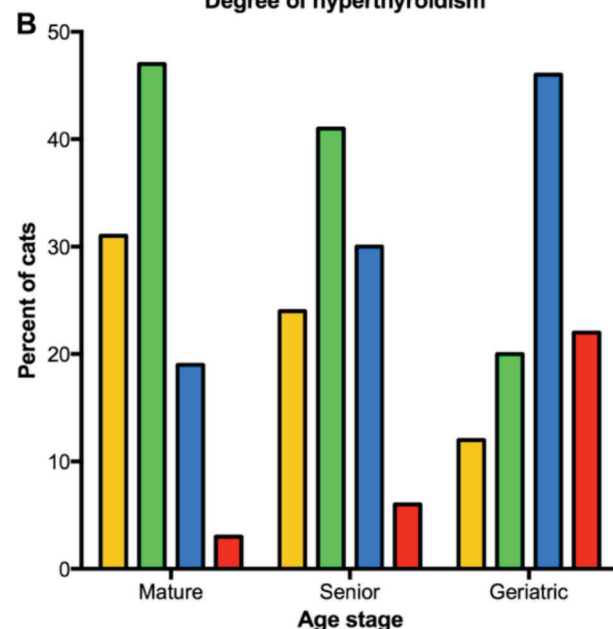
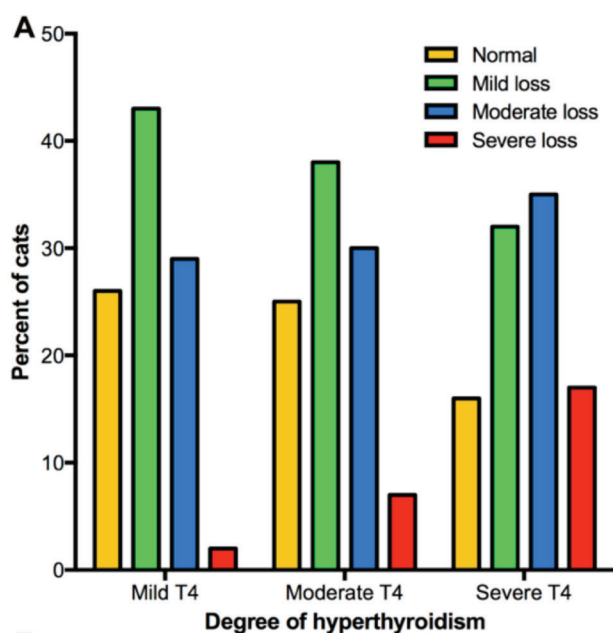


of hyperthyroid cats. Successful treatment leads to weight gain and an increase of BCS in most cats, but almost half fail to regain normal muscle mass. The reason for this is not

Figure 3.* (A) Bar graphs depicting the muscle condition score (MCS) of 462 untreated hyperthyroid cats categorized into three equal-sized groups (n=154) of disease severity (i.e., mild, moderate and severe disease). In each of the three groups, the percentage of hyperthyroid cats with normal muscle mass and mild, moderate and severe muscle loss is depicted. As the severity of hyperthyroid disease increases, notice that the prevalence of normal muscle mass cats decreases while the prevalence of moderate-to-severe muscle wasting increases (P=0.0002).

(B) Bar graphs depicting the MCS of 462 untreated hyperthyroid cats categorized into three groups based on their life stage (mature, senior or geriatric). As the life stage of the cats increases from mature to geriatric, notice that the prevalence of normal muscle mass decreases while the prevalence of moderate and severe muscle wasting increases (P<0.0001).

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known but is likely related to concurrent sarcopenia of aging or concurrent disease and mild cachexia. In addition, some cats may not be fed diets containing enough dietary protein to help rebuild their lost muscle mass.⁴¹

Like hyperthyroidism, uncontrolled diabetes mellitus is a catabolic condition so though obesity predisposes the cat to becoming diabetic, loss of weight, and especially loss of lean body mass, is common in cats with diabetes. At the time of diabetes diagnosis, weight loss is reported in about 70% of cats.⁴² However, cats are more often overweight or obese (40%), than they are normal weight or underweight.^{42,43} Muscle wasting and poor muscle condition scores are detected in about half of cats with diabetes.^{42,43}

Epidemiologic studies in cats consistently show diabetes to be a disease of senior cats. Like cats with hyperthyroidism, the typical diabetic cat is a senior, of which about 70% are more than 10 years of age at the time of diagnosis.^{42,43} Therefore, because most of these cats are senior, they also are prone to developing sarcopenia of aging, as discussed earlier.

In human patients, type 2 diabetes is associated with an increased risk of concurrent sarcopenia.⁴⁴ In addition, because skeletal muscle is a primary site for insulin-mediated glucose uptake and deposition, sarcopenia, and especially sarcopenic obesity,⁴⁴ may promote insulin resistance, predisposing them to the development of type 2 diabetes and making diabetes more resistant to control.^{45,46} It is not known whether the loss of muscle mass alone (sarcopenia) or combined with weight gain (sarcopenic obesity), both commonly seen in cats with diabetes, also contributes to the insulin resistance and hyperglycemia associated with the feline disorder. However, it is reasonable to assume that sarcopenia and sarcopenic obesity may do so in cats as they do in humans.

Clinical Implications for Diagnosis and Treatment of Muscle Wasting in Cats

Severe weight loss and cachexia that develop in a cat with cancer, CKD or advanced heart failure are not a diagnostic dilemma. However, identification of cachexia is more difficult at an earlier stage of disease, when muscle wasting is subtler.

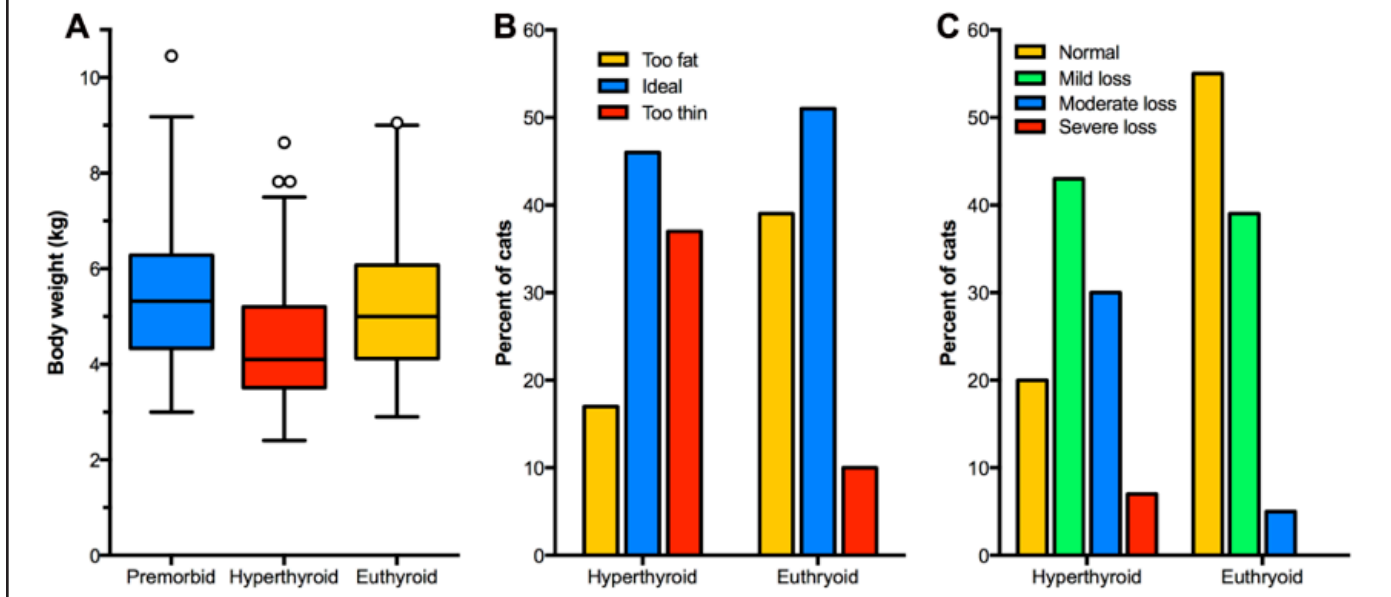
As one may expect, it is important to detect cachexia, sarcopenia or other causes of muscle wasting (e.g., hyperthyroidism or diabetes) in cats in its earliest stages, if possible. To achieve this, body weight, BCS and MCS should be assessed during every physical examination. The goal for BCS in a healthy adult cat should be 4 to 5 on a 9-point BCS scale. Obesity (>7/9 BCS) should be avoided.

Use of a routine MCS also is recommended as part of the routine physical examination in every cat at every visit. Muscle condition scoring systems have been developed for cats, as published by the World Small Animal Veterinary Association.^{25,26} 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, thoracic and lumbar vertebrae, and pelvic bones.

Figure 4.* Before and after body weight, BCS and MCS of 117 cats reevaluated after successful treatment with radioiodine. (A) Box plots of premorbid, hyperthyroid and posttreatment (euthyroid) body weight in 117 cats evaluated before and after treatment with radioiodine. Notice that the cats' premorbid body weight fell significantly ($P < .0001$) when hyperthyroid, whereas the posttreatment euthyroid weight increased significantly ($P < 0.001$) to levels similar to premorbid weight. (B) Bar graphs depicting the percentage of cats with low (too thin), ideal and high (too fat) body condition scores. After treatment, notice that the prevalence of normal and overweight

cats increased while underweight cats decreased ($P < 0.001$). (C) Bar graphs depicting the percentage of cats with normal muscle mass and mild, moderate and severe muscle wasting. After treatment, notice that the prevalence of normal muscle mass increased while mild, moderate and severe muscle wasting decreased ($P < 0.001$). Severe muscle wasting did not persist in any of the cats after treatment.

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BCS and MCS are not directly related as a cat can be obese but still have marked muscle loss, or conversely, a cat can be thin but have normal MCS.

Palpation is required for assessing both BCS and MCS, especially in longhaired cats. Consistently evaluating MCS in all cats will help to identify muscle loss at an early stage (i.e., mild) in aging or ill cats, rather than waiting until muscle loss is moderate or severe, when it may be more difficult to successfully intervene to restore lost muscle tissue.

Several other more objective techniques can be used to estimate body composition, including carcass composition analysis (not ideal for pet cats), deuterium oxide dilution, bioelectrical impedance analysis, quantitative magnetic resonance, ultrasonography, and dual-energy X-ray absorptiometry (DEXA).⁴⁷⁻⁴⁹ Of these, quantitative assessment of muscle using a vertebral epaxial muscle score is one of the most clinically feasible methods for routine analysis of clinical patients for detecting and monitoring the severity of muscle loss in both dogs⁵⁰ and cats (Freeman, LM, personal communication).

For cats with chronic diseases in which weight and/or muscle loss is a component (e.g., CKD, hyperthyroidism, diabetes, cancer, heart disease), a variety of treatments can be used, including careful attention to diet composition.^{22,41} This is particularly important because reduced total caloric and protein intake may be a contributing cause of cachexia and other types of muscle wasting in these patients.^{51,52}

Dietary modification often is beneficial in improving caloric intake and quality of life for these patients, especially in the aging senior or geriatric cat. Although the optimal nutritional profile will vary depending on the individual cat, two factors — calories and protein — are critical to address for all aging cats that show muscle wasting:

(1) Caloric content of food fed: Like people, cats tend to lose weight as they age due to sarcopenia of aging. For cats that are gradually losing weight (or muscle) with aging, a more calorically dense diet should be selected to help prevent weight loss. Caloric content of commercial senior cat diets vary widely, so diets must be carefully selected for the senior cat to achieve and maintain optimal body weight and BCS.

If an aging cat is healthy, in good body condition and eating a good quality, nutritionally balanced diet, there is no reason to change foods due to advancing age alone. If the cat has one of the diseases often seen with aging (hyperthyroidism, diabetes, cancer, dental problems, CKD), adjusting the diet fed (by increasing calories or protein content) may help improve clinical signs or even slow progression of the disease. For cats with CKD, for example, reducing the phosphorus or sodium or avoiding acidic pH (as well as lower protein in advanced azotemic kidney disease) may be beneficial.

(2) Protein intake: Obligate carnivores, such as the cat, are unique in their need for large amounts of dietary protein (specifically, dispensable nitrogen), which distinguishes

them from omnivores and herbivore species.⁵³⁻⁵⁵ This absolute requirement for dietary protein intake in cats is critically important when formulating a diet for cats with muscle wasting. This is especially true in hyperthyroid cats, in which protein catabolism and muscle wasting is universally present.

Assuming adequate calorie intake, protein is the primary macronutrient responsible for maintenance of muscle mass.⁵⁶⁻⁵⁹ Restoring and preserving remaining muscle tissue in cats treated for hyperthyroidism depends on the cat consuming a diet with sufficient amounts of high-quality protein. We recommend a target of 40% or more of daily calories from protein, or greater than or equal to 12 g/100 kcal metabolizable energy (ME).⁴¹ This higher-than-average protein level also helps restore and maintain lost muscle mass because many hyperthyroid cats develop sarcopenia as they age.

The dogma that all senior and geriatric cats should be fed reduced-energy senior diets must be questioned based on what is now known about the increasing energy requirements and nutritional needs of these cats.^{34,36,56,60-62} In most non-obese senior and geriatric cats, logic dictates the use of highly digestible, energy-dense food to mitigate the decline in body weight and lean body tissue and to avoid protein/calorie malnutrition. Reducing protein intake in geriatric cats, at a time when lean tissue has been lost, is contraindicated; when deprived of adequate amounts of dietary protein, carnivores continue to break down muscle tissue to support protein turnover.⁵³⁻⁵⁵ Feeding larger amounts of high-quality protein may help to restore and maintain lost muscle mass in these cats because many develop sarcopenia as they age. However, randomized clinical trials are needed to investigate the role of nutrition as a treatment for older cats with muscle wasting, as has been done for human patients.⁶³

In cats with earlier stages of CKD, phosphorus should be restricted, using methods other than changing to a protein-restricted diet in order to preserve muscle mass as much as possible. In cats with later stages of azotemic CKD, however, use of a prescription kidney diet is recommended. Over-the-counter low-carbohydrate cat foods may have substantially higher phosphate levels than some of the veterinary therapeutic diets designed for diabetes. Therefore, the nutrient profile of the specific product must be obtained to determine whether the product meets the desired nutrient goals for that patient.

Potential Future Treatments for Muscle-Wasting Diseases

Because of the important implications of cachexia and sarcopenia on morbidity and mortality in human patients, there is extensive research into the prevention, diagnosis and treatment of these syndromes. In addition to nutritional modification and exercise, there is ongoing research for new and effective treatments in cachexia and sarcopenia to prevent and even reverse muscle loss.⁶⁴ Most current research

is focused on drugs aimed at enhancing food intake and increasing muscle mass and function.

One promising new class of drugs is the growth hormone secretagogues (GHS) — a class of small molecule compounds discovered in the mid-1990s that stimulate the release of growth hormone (GH) and may be useful in treatment of anorexia and cachexia.⁶⁵ It was subsequently discovered that GHS compounds mimic ghrelin, the hormone that is secreted from endocrine cells in the stomach and stimulates appetite and food intake in humans.⁶⁶

Capromorelin is an oral active ghrelin receptor agonist that mimics the action of ghrelin and acts directly on the hunger centers of the hypothalamus to stimulate appetite and enhance food consumption.⁶⁵ The FDA recently approved capromorelin (ENTYCE[®], Aratana Therapeutics) as a new drug for use in dogs as a ghrelin receptor agonist. Capromorelin oral solution has been shown to increase food consumption, body weight, GH, and insulin-like growth factor 1 (IGF-1) secretion in healthy laboratory Beagle dogs.^{67,68} Preliminary studies indicate that capromorelin also increases food intake and promotes weight gain in laboratory cats,⁶⁹ but only limited peer-reviewed research studies on cats have been published to date.⁷⁰

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