Sarcopenia of ageing and cachexia in dogs and cats

Valerie J. Parker, DVM, DACVIM, DACVN
Associate Professor – Clinical
Department of Veterinary Clinical Sciences
The Ohio State University Veterinary Medical Center
United States of America

Before specifically discussing sarcopenia and cachexia, a reminder about the importance of a general nutritional assessment of every dog and cat presented to the veterinarian will be presented. This should include assessment of 1) the animal, including its medical condition(s); 2) its diet; and 3) the feeding method. Animal assessment should include a body weight, body condition score (BCS) and muscle condition score (MCS). Various medical conditions will influence predilections for alterations in body composition as well as optimal nutritional management of a patient.

Assessment of lean body mass is an integral part of every clinical examination.

A thorough diet history includes obtaining details about the amounts fed of the animal's primary diet(s), including specific brand and variety, types of treats, table foods and foods used for medication administration, as well as any dietary supplements the animal is receiving. Sarcopenia is defined as muscle loss associated with age, specifically in the absence of disease. In people, sarcopenia is influenced by physical inactivity, increased cytokine production (eg, tumor necrosis factor [TNF], interleukin [IL]-6), IL-1), decreased protein synthesis and altered hormone concentrations.[1-3] While sarcopenia has been recognized in veterinary medicine, little is known about the etiology of its development or how to address it in a clinical patient population. What is known will be addressed below.

Sarcopenia is a muscle loss associated with age.

In dogs and cats, increasing age has been shown to affect changes in all aspects of body composition, including body weight, BCS, a marker of body fat, and MCS, a marker of muscle mass. In one lifetime study of dogs, progressive loss of lean muscle mass was documented to begin between 9 and 11 years of age.[4] Increasing age has been shown to be negatively correlated with body weight, BCS and MCS in cats with a variety of diseases.[5-7] In cats that develop chronic kidney disease (CKD), weight loss may be observed for up to 3 years prior to diagnosis.[6] This highlights the importance of serial body composition assessment as it may increase suspicion of impending or current undiagnosed disease.

Assessing muscle loss requires visual examination and palpation of the spine, scapulae, skull and wings of the ilia. It is currently recommended to score MCS either as normal or with variable degree of atrophy (i.e., mild, moderate, severe).[8] There is some subjectivity associated with this method; thus, additional tools have been developed to more objectively score MCS. In people, despite the availability of several modalities to measure muscle (e.g., bioelectric impedance [BIA], dual-energy-X-ray absorptiometry [DEXA], computed tomography [CT] and magnetic resonance imaging [MRI]), there is no consensus about which is "best." For example, while DEXA is relatively inexpensive and easily performed, it lacks specificity to determine how much of the fat-free mass is actually muscle mass.[9] Conversely, CT and MRI can better distinguish this nuance, but they are more expensive and less clinically accessible tests.[9,10] In dogs and cats, ultrasound and CT have been reported to accurately measure muscle mass in dogs and cats. [11-13,a] Recently the term Vertebral Epaxial Muscle Score (VEMS) was proposed to represent the ultrasound technique of assessing epaxial muscle mass.[12]

The exact mechanism(s) for sarcopenia in veterinary medicine remains to be determined. It is likely that many documented changes in people occur in dogs and cats (e.g., decreased activity, increased protein turnover). One study evaluated for histologic and immunohistochemial changes in skeletal muscles of dogs of different ages.[14] Muscle atrophy was present in all 25 geriatric dogs (15-20 years old) and none of the young control dogs (≤ 5 years old). In addition to atrophy, the most significant histologic changes included mitochondrial abnormalities and the presence of lipofuscines inside the muscle fibers, a consequence of reactive oxygen species (ROS)-induced damage. Additionally, there was increased expression of two markers of autophagy (Beclin-1 and microtubule-associated protein light chain 3 [LC3]-II).[14] There is still much work to be done to further elucidate the microscopic details that affects muscle loss in dogs and cats.

Cachexia is muscle loss that occurs in the presence of disease (e.g., chronic kidney disease [CKD], cardiac disease, neoplasia, chronic enteropathies). Significant muscle loss can also occur secondary to either endogenous or exogenous corticosteroid administration. There is constant debate over the exact definition of cachexia, and various schemas have been proposed. One of the hallmarks of the diagnosis is the presence of inflammation contributing to weight loss. Additional factors include decreased muscle strength, fatigue, anorexia and various hematology and biochemistry abnormalities (e.g., anemia, hypoalbuminemia).[15,16]

Cachexia is muscle loss that occurs in the presence of disease.

While it is challenging to specifically assess muscle strength in dogs and cats, evidence suggests that animals that can maintain weight better in the face of chronic inflammatory conditions have improved survival. This relates to "the obesity paradox" that has been described in people and dogs and cats with various diseases.[17-21] Despite overweight/obesity predisposing to some diseases, once a chronic, wasting condition is diagnosed, maintaining extra weight has been shown to confer survival benefits. This is thought to be due to better maintenance of lean muscle mass, or in other words, lack of cachexia.[18,22] It remains to be determined what specifically affords some people or animals a better ability to maintain weight and muscle. Effective management of muscle loss remains elusive. In some cases, correction of underlying disease, or removal of a specific inciting cause (e.g., corticosteroid administration) may help. However, muscle mass is usually not regained as easily as fat mass is. In one study of treated hyperthyroid cats, both BCS and MCS improved, but many cats retained some degree of muscle atrophy.[7]

Both dietary and pharmacologic interventions have been studied in relation to sarcopenia and cachexia in people. Various macronutrient profiles have been examined to determine what can positively influence muscle mass. Much emphasis has been placed on maintenance of adequate dietary protein intake, as well as various sources of protein and additional amino acid supplementation. In one randomized, double-blind, placebo-controlled trial in frail elderly people, supplementation with a milk protein concentrate, in addition to resistance training, helped increase muscle mass.[23] However other systematic reviews have shown mixed results in elderly people receiving protein supplementation in addition to resistance training.[24,25] Although there is not a consistent increase in muscle mass, there does seem to be a greater trend toward improved muscle strength.[24,25] Additionally, there is no consensus about the best source of this protein supplementation (e.g., meat vs. dairy vs. soy). Some authors suggest that meat and dairy-based protein sources are best due to their inherent essential amino acid profiles.[26] In one study, soy supplementation did not augment muscle mass in elderly people undergoing resistance training (as compared to dairy protein supplementation).[27] More research in veterinary medicine is needed to determine how additional dietary protein influences maintenance (or improvement) of muscle mass.

Fish oil supplementation in dogs reduced cardiac cachexia.

Fish oil has been touted as a beneficial source of anti-inflammatory omega-3 polyunsaturated fatty acids (n-3 PUFA), eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA).[28,29] In dogs, fish oil supplementation reduced cardiac cachexia.[30] In addition to reducing inflammation-mediated muscle loss, EPA has been shown to reduce muscle breakdown via the ubiquitin-proteasome proteolytic pathway.[31] There is some evidence to suggest that they exert an anabolic effect on muscle, at least partially by increasing activation of the mTOR-p70s6k signaling pathway, a control point for muscle cell growth.[32] A metaanalysis in people was unable to show great benefit from fish oil supplementation;[33] however, side effects and cost are relatively low, thus it seems reasonable to continue offering this as a supplement to veterinary patients as long as it is tolerated.

Additionally, various vitamins, minerals and antioxidants have been studied to determine what optimal supplementation is in management of muscle wasting.[34] Some studies suggest that supplementation with vitamin D,[35] magnesium and vitamins C and E may help improve lean muscle mass.[32,35,36] More work needs to be done, both in people and in animals, to be able to draw specific conclusions about these supplements.

Ghrelin and ghrelin mimetics, also known as growth hormone secretagogues, have been used in people and animals to improve food intake, body weight and lean muscle mass.[37-39] One pilot study evaluated the effects on muscle mass using a myostatin antagonist in dogs with congestive heart failure and cardiac cachexia. While 3 out of 6 dogs did have improvement in MCS, the results were not statistically significant. The authors proposed that longer-term, randomized controlled clinical trials were warranted to further assess treatment efficacy.[40]

Some potential new areas for management of sarcopenia and cachexia include exercise therapy and, possibly, regenerative cell therapy. The field of veterinary sports medicine and rehabilitation is relatively new, and studies are needed to objectively measure outcome as it relates to muscle mass and strength. Regenerative cell therapy is gaining more popularity in both human and veterinary medicine, but much more research is needed to determine what (if any) benefits may be related to improving muscle mass and function.[41]

Conclusions

Muscle loss is commonly detected in dogs and cats. It is affected by a number of factors, including an animal's individual metabolism, underlying disease(s), and dietary intake of protein and other nutrients. Effective management of muscle loss, both sarcopenia and cachexia, requires additional research to further elucidate specific mechanisms by which muscle loss and growth are affected and how to modify nutritional, pharmacologic and environmental factors to positively impact muscle condition, strength and ultimately longevity.

References:

1. Boirie Y. Physiopathological mechanism of sarcopenia. *J Nutr Health Aging* 2009;13:717-723.
2. Fry CS, Rasmussen BB. Skeletal muscle protein balance and metabolism in the elderly. *Curr Aging Sci* 2011;4:260-268.
3. Dalle S, Rossmeislova L, Koppo K. The role of inflammation in age-related sarcopenia. *Front Physiol* 2017;8:1045.
4. Lawler DF, Larson BT, Ballam JM et al. Diet restriction and ageing in the dog: major observations over two decades. *Brit J Nutr* 2008;99:793-805.
5. Michel KE, Anderson W, Cupp C et al. Correlation of a feline muscle mass score with body composition determined by dual-energy X-ray absorptiometry. *Brit J Nutr* 2011;106 Suppl 1:S57-59.
6. Freeman LM, Lachaud MP, Matthews S et al. Evaluation of Weight Loss Over Time in Cats with Chronic Kidney Disease. *J Vet Intern Med* 2016;30:1661-1666.
7. 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.
8. WSAVA website. Muscle Condition Score. Available at: https://www.wsava.org/sites/default/files/Muscle%20condition%20score%20chart-Cats.pdf . Accessed January 25, 2018.
9. Buckinx F, Landi F, Cesari M et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. *J Cachexia Sarcopenia Muscle* 2018. DOI: 10.1002/jcsm.12268
10. Teigen LM, Kuchnia AJ, Mourtzakis M et al. The use of technology for estimating body composition: Strengths and weaknesses of common modalities in a clinical setting *Nutr Clin Pract* 2017;32:20-29.
11. Hutchinson D, Sutherland-Smith J, Watson AL et al. Assessment of methods of evaluating sarcopenia in old dogs. *Am J Vet Res* 2012;73:1794-1800.
12. Freeman LM, Sutherland-Smith J, Prantil LR et al. Quantitative assessment of muscle in dogs using a vertebral epaxial muscle score. *Can J Vet Res* 2017;81:255-260.
13. Sakaeda K, Shimizu M. Use of B-mode ultrasonography for measuring femoral muscle thickness in dogs. *J Vet Med Sci* 2016;78:803-810.
14. Pagano TB, Wojcik S, Costagliola A et al. Age related skeletal muscle atrophy and upregulation of autophagy in dogs. *Vet J* 2015;206:54-60.
15. Evans WJ, Morley JE, Argiles J et al. Cachexia: a new definition. *Clin Nutr* 2008;27:793-799.
16. Muscaritoli M, Anker SD, Argiles J et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr* 2010;29:154-159.
17. Park J, Ahmadi SF, Streja E et al. Obesity paradox in end-stage kidney disease patients. *Prog Cardiovasc Dis* 2014;56:415-425.
18. Lavie CJ, McAuley PA, Church TS et al. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol* 2014;63:1345-1354.
19. Slupe JL, Freeman LM, Rush JE. Association of body weight and body condition with survival in dogs with heart failure. *J Vet Intern Med* 2008;22:561-565.
20. Finn E, Freeman LM, Rush JE et al. The relationship between body weight, body condition, and survival in cats with heart failure. *J Vet Intern Med* 2010;24:1369-1374.
21. Parker VJ, Freeman LM. Association between body condition and survival in dogs with acquired chronic kidney disease. *J Vet Intern Med* 2011;25:1306-1311.
22. Antonopoulos AS, Tousoulis D. The molecular mechanisms of obesity paradox. *Cardiovasc Res* 2017;113:1074-1086.
23. Tieland M, Dirks ML, van der Zwaluw N et al. Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: A randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2012;13:713-719.
24. Finger D, Goltz FR, Umpierre G et al. Effects of protein supplementation in older adults undergoing resistance training: A systematic review and meta-analysis. *Sports Med* 2015;45:245-255.
25. Thomas DK, Quinn MA, Saunders DH et al. Protein supplementation does not significantly augment the effects of resistance exercise training in older adults: A systematic review. *J Am Med Dir Assoc* 2016;17:959.e1-959.e9.
26. van Vliet S, Burd NA, van Loon LJC. The skeletal muscle anabolic response to plant- versus anima-based protein consumption. *J Nutr* 2015;145:1981-1991.
27. Thomson RL, Brinkworth GD, Noakes M et al. Muscle strength gains during resistance exercise training are attenuated with soy compared with dairy or usual protein intake in older adults: A randomized controlled trial. *Clin Nutr* 2016;35:27-33.
28. LeBlanc CJ, Horohov DW, Bauer JE et al. Effects of dietary supplementation with fish oil on in vivo production of inflammatory mediators in clinically normal dogs. *Am J Vet Res* 2008;69:486-493.
29. Bauer JE. Therapeutic use of fish oils in companion animals. *J Am Vet Med Assoc* 2011;239:1441-1451.
30. Freeman LM, Rush JE, Kehayias JJ et al. Nutritional alterations and the effect of fish oil supplementation in dogs with heart failure. *J Vet Intern Med* 1998;12:440-448.
31. Pappalardo G, Almeida A, Ravasco P. Eicosapentaenoic acid in cancer improves body composition and modulates metabolism. *Nutrition* 2015;31:549-555.
32. Smith GI, Atherton P, Reeds DN et al. Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial. *Am J Clin Nutr* 2011;93:402-412.
33. Ries A, Trottenberg P, Elsner F et al. A systematic review on the role of fish oil for the treatment of cachexia in advanced cancer: An EPCRC cachexia guidelines project. *Palliative Med* 2011;26:294-304.
34. Abiri B, Vafa M. Nutrition and sarcopenia: A review of the evidence of nutritional influences. *Crit Rev Food Sci Nutr* 2017:1-11.
35. Bauer JM, Verlaan S, Bautmans I et al. Effects of a vitamin D and leucine-enriched whey protein nutritional supplement on measures of sarcopenia in older adults, the PROVIDE study: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc* 2015;16:740-747.

36. Welch AA. Nutritional influences on age-related skeletal muscle loss. *Proceedings of the Nutrition Society* 2014;73:16-33.
37. Ali S, Chen JA, Garcia JM. Clinical development of ghrelin axis-derived molecules for cancer cachexia treatment. *Curr Opin Support Palliat Care* 2013;7:368-375.
38. Zollers B, Wofford JA, Heinen E et al. A prospective, randomized, masked, placebo-controlled clinical study of capromorelin in dogs with reduced appetite. *J Vet Intern Med* 2016;30:1851-1857.
39. Rhodes L, Zollers B, Wofford JA et al. Capromorelin: a ghrelin receptor agonist and novel therapy for stimulation of appetite in dogs. *Vet Med Sci* 2017: doi:10.1002/vms3.83.
40. Freeman LM, Rush JE, Cunningham SM et al. Pilot study of a myostatin antagonist in dogs with cardiac cachexia. *J Vet Cardiol* 2015;17:210-215.
41. Naranjo JD, Dziki JL, Badylak SF. Regenerative medicine approaches for age-related muscle loss and sarcopenia: A mini-review. *Gerontology* 2017;63:580-589.