The processes and manifestations of aging can be considered at multiple levels. Clinicians naturally focus on the organismal level and the impact of aging on health and physical function. Geroscience researchers have focused more on the cellular and molecular levels, looking for primary mechanisms that may be said to cause aging. The bridge between these is the level of tissues and organ systems. The activity of aging mechanisms at the cellular and molecular level manifests in tissues and organ systems, and these manifestations are ultimately responsible for the clinical phenotypes that emerge in the organism. At each of these levels, there are complex interactions between multiple physiologic pathways, individual genetic background, and environmental influences, and there is always a stochastic element to the emergence of clinical abnormalities from the multifaceted process of aging.

The purpose of this manuscript is to consider key hallmarks of aging and how these manifest at the level of tissues and organ systems and also to identify important knowledge gaps in veterinary geroscience. Most of the evidence concerning aging mechanisms and clinical phenotypes comes from animal models (predominantly worms, flies, and rodents) and research in humans, so this review will emphasize areas where further investigation is needed to elucidate how these mechanisms apply in dogs and cats. A companion Currents in One Health review in the June 2022 issue of the Journal of the American Veterinary Medical Association describes the clinical phenotype of physical and behavioral aging in dogs and the impact of aging on the welfare of companion dogs and on their human caregivers.

General Principles of Veterinary Geroscience

There is no single consensus definition of aging, but it is typically characterized by the increasing risk of disease, dysfunction, and death over time.¹ On a physiologic level, this entails the loss of robustness (the ability to resist deviation from an original or optimal state) and resilience (the ability to return to this state after deviations induced by external stressors).² There is no single pathway or mechanism that causes aging or all age-related health outcomes. There are many relevant pathways, and the importance of each varies by species, genetic background, ontogeny, and environmental context. The goal of geroscience is to understand the biology of aging well enough to extend life and mitigate the negative impacts of aging on health and function.
There is extensive research evidence identifying cellular and molecular mechanisms of aging, which are consistent across varied taxa. The most critical research gaps in veterinary geroscience include the details of specific aging mechanisms at all levels in individual veterinary species and an understanding of the links between levels in each species: cellular/molecular ⇔ tissue/organ system ⇔ clinical phenotype.

**Cellular and Molecular Hallmarks of Aging**

The concept of aging as an inevitable and inscrutable process has been overturned by decades of research illustrating mechanisms of aging common to many different species. The specific manifestations of aging may differ between species and individuals, but the general processes of aging are similar and well described.

The most frequently used system for categorizing these is the set of hallmarks of aging proposed by López-Otín et al. These mechanisms are thought to underlie many of the phenotypic changes seen with aging in various species. These mechanisms can also influence the life span and health span of organisms when manipulated experimentally. Although additional mechanisms of aging, and complex interaction effects between these hallmarks, are still being discovered and characterized, these are the most widely studied potential targets for interventions to extend life span and health span. Several authors have reviewed what is known about the role these hallmarks play in canine aging. There is considerably less information regarding the role of these mechanisms in feline aging.

**Genetic damage**

Accumulated damage in somatic, germline, and mitochondrial DNA is associated with aging, and experimental induction of such damage can cause accelerated aging. Factors that prevent or ameliorate DNA damage, whether naturally occurring or derived clinical interventions, may retard or even reverse age-associated disease and dysfunction, although there is yet little direct experimental evidence demonstrating this in dogs or cats.

There is also little research elucidating the role of DNA damage or defects in DNA repair mechanisms in producing aging changes in cats and dogs. However, the similarities between the genomes and DNA repair systems of these species and other mammals, such as humans and mice, in which the role of DNA damage in aging is better studied, and the existence of common genetic abnormalities associated with age-associated neoplasia in these species, suggest that DNA damage is likely a relevant factor in canine and feline aging.

**Telomere attrition**

Telomeres are repetitive noncoding base sequences at the ends of chromosomes that maintain chromosome integrity during cell division and replication. These shorten with each replication event in the absence of the reparative enzyme telomerase, which is not usually present in somatic cells. When telomeres become too short, this leads to DNA damage and cellular stress, which can then trigger a dysfunctional, nonreplicative cellular state called senescence. These structures are considered a hallmark of aging because telomere shortening accompanies aging, and accelerated aging is associated with telomerase deficiency or induced telomere attrition. Interventions to protect and repair telomeres have extended life span in experimental animals.

Research has shown that telomeres shorten with age in dogs much more rapidly than in humans at a ratio roughly corresponding to the difference in average life span between the species. The length of telomeres also differs between breeds, and those breeds with longer telomeres tend to have longer life span than breeds with shorter telomeres. These findings support the importance of telomere attrition in canine aging. Research has also demonstrated telomere shortening with aging in cats and associated shorter telomeres with chronic kidney disease, one of the most significant age-associated diseases in this species.

**Epigenetic changes**

Epigenetic changes are modifications to DNA other than change in the base-pair sequence, such as methylation. Such changes influence gene expression without directly altering the genes themselves. These changes occur with aging and can have deleterious effects on gene products and health. Epigenetic change has been intensively explored as a potential measure of biological age (the extent of changes with time in specific physical, behavioral, and cellular or biochemical manifestations of aging). Epigenetic “clocks” have been developed for dogs, and these can predict chronological age and, potentially, biological age. The life span difference between large and small breeds also appears to be reflected in differences in age-associated epigenetic changes between breeds. Epigenetic clocks have also been developed for domestic cats, although there is little work investigating how these reflect biological age, health status, or mortality risk or whether these clocks could help assess the impact of therapies to slow aging.

**Dysfunctional proteostasis**

Proteostasis is the maintenance of normal protein structure and distribution in cells and tissues, which is necessary for normal protein function. Numerous coordinated mechanisms are constantly working to maintain protein homeostasis. Derangements in protein structure and accumulation of aberrant proteins are other hallmarks of aging that have been associated with chronological age and implicated in age-associated disease. Laboratory animal studies have shown mitigation of aging phenotypes with genetic manipulations to improve proteostasis. There is limited evidence indicating dogs share
mechanisms for preserving protein stability and removing dysfunctional proteins with humans and other mammals, and this likely indicates similarity in the role of deficient proteostasis in aging between dogs and other species.4

There are no studies directly investigating changes in proteostasis as a mechanism of aging in cats. However, cats do show accumulation of lipofuscin in various tissues and aggregation of abnormal proteins in the brain with advancing age, similar to many other species, and this may reflect changes in the ability to maintain normal protein structure and prevent accumulation of deleterious proteins.11

Changes in nutrient signaling

One of the most studied systems involved in aging across species is nutrient signaling—the pathways regulating cellular metabolism and the relationship between metabolic activity and nutrient availability. These pathways include the somatotropic axis, involving growth hormone (GH) and insulin-like growth factor-1 (IGF-1); insulin and other factors regulating glucose metabolism; mechanistic target of rapamycin (mTOR); a serine/threonine protein kinase, involved in regulation of protein metabolism; and systems that sense energy and nutrient scarcity, such as adenosine monophosphate kinase and the sirtuins.12

Nutrient-sensing mechanisms are key targets for efforts to extend life span and health span, and there is substantial evidence that manipulations of these systems can prolong life and reduce disease in many species. Interventions such as dietary restriction and pharmacologic agents that interact with nutrient-sensing systems have had clear, beneficial effects on life span and age-associated disease. For example, caloric restriction has been shown to extend life by up to 15% in Labrador Retrievers and to reduce the occurrence of age-associated disease and biomarkers related to nutrient-sensing systems.12 Furthermore, established differences in body size and life span have been linked to genes associated with the somatotropic axis and other elements of nutrient-sensing systems in dogs.4,5

Very few data are available regarding the somatotropic axis in cats, and none explicitly linking it with aging and life span. Levels of GH and IGF-1 have been associated with metabolic dysfunction (eg, insulin resistance) and overt disease (eg, diabetes mellitus, hypertrophic cardiomyopathy). However, the relationships uncovered so far are complex and inconsistent, so no firm conclusions can yet be drawn about the role of nutrient-sensing pathways in feline aging.13,14

There are also no caloric restriction studies available to indicate the impact of this intervention of aging biomarkers or life span in cats. One intriguing study15 did show that cats on a diet supplemented with a variety of antioxidants, prebiotics, and essential fatty acids lived significantly longer than cats fed control diets. In this study, all cats were fed ad libitum. However, those in the group that had the longest life span lost less weight as they aged than those with a shorter life span despite the fact that their food consumption increased significantly less over time than the cats in those groups. This pattern is counterintuitive, and the precise significance is unclear, but it could suggest a positive relationship between longevity and lower food consumption.15,16

The relationship between body weight, body condition, and life span in cats appears to be different from that in dogs. While larger size and overweight body condition are clearly associated with shorter life span in dogs,7,17,18 this association is not as well-established in cats. One study19 suggested that larger size is associated with shorter life span, although the distinction between body size and body condition was not evaluated. In contrast, another study20 found that maximum body condition scores considered overweight were associated with greater longevity than optimal, underweight, or extremely obese body condition. Furthermore, loss of both lean and fat mass in cats occurs after about 12 years of age, and this general decline in body weight appears to be a causal factor or signal of an age-associated increase in morbidity and mortality risk.20,21 Although limited, these data suggest that cats may exhibit a different relationship between nutrient-sensing systems and aging than dogs and humans.

Mitochondrial dysfunction

Another key mechanism of aging includes impaired functioning of mitochondria, which involves increased oxidative damage to DNA and cells and decreased energy available for normal functions and homeostatic mechanisms. Mitochondrial dysfunction has been particularly implicated in the development of age-associated neurodegenerative diseases. Limited research has suggested differences in mitochondrial function and markers of oxidative damage between old and young laboratory Beagles, and there is some evidence that reactive oxygen species and cognitive dysfunction can be reduced by antioxidant therapy.22 However, not all studies support this association.4 There is also in vitro evidence showing differences in mitochondrial function and oxidative metabolism between dog breeds with shorter and longer life spans, suggesting a possible role for mitochondria in determining life span in dogs.23

Again, there are few data concerning changes in mitochondrial function or oxidative damage in aging in cats. Basic research has established reference values for some markers of oxidative stress,24 and markers of increased oxidative stress or impaired antioxidant capacity have been associated with some age-associated diseases, such as chronic kidney disease and hypertrophic cardiomyopathy,25,26 but no direct evidence links aging, mitochondrial dysfunction, and oxidative damage in cats.

Cellular senescence

Another aging mechanism conserved across species is cellular senescence. Cells exhibit cell-cycle arrest and characteristic changes in metabolism and intercellular signaling when DNA damage, telomere attrition, or other factors trigger senescence. This
has beneficial effects in preventing propagation of abnormal cells. However, if senescent cells are not effectively removed and replaced, their accumulation may contribute to the manifestations of aging.

Senescent cells may also develop a senescence-associated secretory phenotype (SASP), a state of increased production of proinflammatory cytokines and other compounds, contributing to the age-associated chronic low-grade inflammatory condition known as inflammaging.27 There is some research on accumulation or functions of senescent cells in dogs and cats, but so far the true impact of this aging mechanism in these species has not been conclusively established.3,4

**Stem cell depletion and dysfunction**

Several of the mechanisms of aging already discussed converge in the loss of functional stem cells, which experience senescence and age-associated damage just as differentiated cell types do but are critical to the renewal and repair of body tissues. Loss of this regenerative capacity is the proximate cause of multiple manifestations of aging.

There has been abundant research into sources and applications for canine stem cells, although this has been in the context of treatment for specific diseases rather than aging as a general phenomenon.28 This research suggests great potential for stem cell therapies in mitigation of age-associated diseases. However, the clinical use of insufficiently tested stem cell treatments has far outpaced the research evidence for efficacy, and there is much work to be done before validated and reliably effective treatments will be available.

**Altered intercellular signaling and inflamming**

Finally, altered intercellular communication often develops with aging, manifesting most dramatically in inflamming, a chronic inflammatory state that increases the risk of many age-associated diseases. Other manifestations of defective intercellular signaling include perturbations of the hypothalamus-pituitary-adrenal axis, immunosenescence, and potentially alterations of the microbiome, which can influence organ function throughout the body. There is limited evidence that dogs and cats experience age-associated increases in inflammation and diminished immune function,4,29,30 that inflamming may be involved in the pathogenesis of some age-associated diseases,31 and that antiaging interventions, such as dietary restriction, may mitigate these changes.12,32

**Aging at the Level of Tissues**

Aging affects every tissue and organ system, and a comprehensive review of all possible mechanisms would be impracticable. This review will focus on three representative tissues that play particularly significant roles in the global process of physical aging and in the clinical manifestations of age-related decline in dogs and cats. These include musculoskeletal tissues (muscle, bones, and joints), brain tissue, and adipose tissue.

**Musculoskeletal system**

Changes in the makeup and function of muscle, bone, and joints are common and characteristic aspects of aging. As robustness and resilience decline with age, the capacity of these tissues to regenerate and repair is degraded and the equilibrium between anabolic and catabolic processes is lost. This eventually leads to the loss of mass and function in these tissues and ultimately clinical disorders such as sarcopenia, osteoporosis, and osteoarthritis (OA). Several core-aging mechanisms appear in the pathophysiology of these and other tissues and organ systems, highlighting their general importance in aging. These include a shift from anabolism to catabolism, diminished stem cell capacity, metabolic derangement, and deleterious chronic inflammation.

**Aging changes in skeletal muscle**

Aging is associated with significant changes in the structure, function, and total mass of skeletal muscle (Figure 1). In humans, these changes often culminate in the clinical condition of sarcopenia, a progressive and generalized loss of skeletal muscle mass and function. Sarcopenia is associated with global functional decline, frailty, and increased mortality risk.33

Dogs exhibit generalized sarcopenia with loss of total muscle mass as seen in humans and rodents.34 Subjectively, veterinarians and owners perceive dogs to lose strength and functional capacity with age, but specific measurements of changes in muscle strength with age, as performed in humans and laboratory animals, have not been published. The detailed clinical features and diagnostic criteria of sarcopenia in dogs remain undefined.35 Sarcopenia is also a recognized condition in cats, but there is very little evidence available to characterize it or support specific causal hypotheses.16,35

The pathophysiology of sarcopenia is complex and incompletely understood, but key elements have been identified, largely through studies in humans and rodents. The imbalance in anabolic and catabolic pathways leading to sarcopenia is generated by multiple interacting mechanisms. Hormonal factors, such as decreasing levels of GH, IGF-1, and the sex hormones estrogen and testosterone, reduce muscle growth and regeneration in humans.36

A key factor in the loss of muscle mass is the presence of low-grade chronic inflammation, a mechanism common to many age-related pathologies. High levels of the proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in particular are associated with the development of sarcopenia in humans.37

The role of chronic inflammation in canine sarcopenia is unclear. Chronic elevation of cytokines associated with sarcopenia, such as TNF-α and IL-6, has not been documented in dogs, and the limited research available so far does not clearly demonstrate that dogs exhibit the chronic low-grade
inflammation seen in elderly humans. Some in vitro and cross-sectional in vivo evidence suggests there may be an increase in relevant inflammatory cytokines and other markers of inflammation in older cats, but the evidence is sparse and inconsistent and has not been linked to changes in lean body mass.

Systemic insulin resistance is both a cause and a consequence of sarcopenia. Insulin has anabolic effects on skeletal muscle, and the loss of insulin sensitivity with age reduces this stimulus for muscle tissue production and maintenance. Conversely, skeletal muscle is the largest sink for glucose in the body, and reduced insulin sensitivity in muscle tissue leads to increases in both glucose and insulin levels. Chronic hyperinsulinemia and reduced insulin sensitivity are also proinflammatory conditions that exacerbate the negative effects of chronic inflammation on muscle mass. The metabolic dysfunction associated with insulin resistance, and the activity of aging adipose tissues, which is discussed below, contribute to the infiltration of muscle cells with lipids, which further impairs function and contributes to catabolism.

There is some indirect evidence that insulin resistance does play a role in canine sarcopenia despite the notably lower incidence of hyperglycemia and diabetes mellitus in this species compared with humans and cats. Insulin resistance is documented to increase in aging dogs concurrent with loss of lean body mass. Caloric restriction preserves both insulin sensitivity and lean body mass in dogs. This would be compatible with the demonstrated reciprocal link between sarcopenia and insulin resistance described in humans and rodents.

It is unknown what role, if any, insulin metabolism plays in feline muscle aging. There is a relatively high incidence of diabetes mellitus in this species, and muscle wasting is common in cats with this disorder, but the relationship between aging, insulin metabolism, and age-associated sarcopenia in the absence of overt diabetes is unclear.

Aging in humans and rodents is also characterized by the loss of muscle satellite cells, the stem cells that are necessary for muscle repair and regeneration. Prolonged quiescence and the accumulation of waste products and nonfunctional organelles, especially mitochondria, in satellite cells are seen with aging in rodents and humans and appear to be associated with decreased regenerative capacity and loss of muscle mass. Such loss of stem cell-mediated regenerative potential is a common hallmark of aging across many tissues.

Limited evidence suggests no loss of satellite-cell proliferative capacity in the muscles of aged dogs compared with young dogs, although there may be differences in antioxidant capacity. It is unclear the extent to which aging affects the number and function of satellite cells in this species, and there is no evidence identifying changes in muscle stem cell number or function with aging in cats.

Skeletal muscle is a tissue with high-energy demands, and appropriate mitochondrial number and function are critical to normal muscle function. Decline in the number of mitochondria, along with redistribution and impaired function, is an important

Figure 1—Key mechanisms and manifestations of muscle tissue aging. GH = Growth hormone. IGF-1 = Insulin-like growth factor-1. IL-6 = Interleukin-6. TNF-α = Tumor necrosis factor-α.
feature of sarcopenia leading to loss of muscle function. There is also a shift in muscle fiber types from type I (oxidative) to type II (glycolytic), due primarily to loss of type II fibers. This has the functional consequences of reducing muscle strength even when overall muscle mass is preserved. Selective loss of type II muscle fibers and abnormal distribution and function of mitochondria have been documented in dogs but not in cats.

Finally, physical activity is a critical component to the maintenance of normal muscle mass and function. Activity tends to decline with aging, due to changes in energy metabolism, muscle strength, behavior and nervous system functioning, and pain or disability associated with age-related disease. Inactivity exacerbates insulin resistance, chronic inflammation, and prolonged quiescence of satellite cells, all of which contribute to declining muscle mass and function.

The impact of physical activity on aging processes in canine and feline muscle tissue is an area in need of further investigation. Dogs respond to cardiovascular conditioning and strength-training exercise with similar physiologic adaptations as humans, increasing their aerobic fitness and strength. Cats can respond to strength training with muscle development, but it is unclear whether they adapt to forced aerobic exercise in the same way dogs and humans do.

Unfortunately, there is virtually no research evidence directly evaluating the impact of exercise interventions on health outcomes or longevity in cats or dogs.

Given the remarkable consistency in general hallmarks and mechanisms of aging among mammals, it is likely that many of the mechanisms described in other species are relevant to muscle aging in dogs and cats. To move forward with clinical assessment tools and interventions to prevent and ameliorate sarcopenia in these species, further research is needed to characterize the cellular and molecular mechanisms and clinical phenotype of canine and feline sarcopenia and to identify potential therapeutic targets.

**Aging changes in bones**

Bone mass is maintained by a balance between osteoclast and osteoblast activity, similar to the balance between catabolic and anabolic processes that maintain muscle tissue (Figure 2). Aging involves a general loss of bone mass and density due to a shift toward increased osteoclast activity and turnover and decreased bone formation by osteoblasts in response to mechanical loading. In humans and rodents, this eventually leads to clinically significant osteopenia and often osteoporosis.

Unlike the species in which bone aging has been most extensively studied, humans and rodents, dogs and cats do not develop clinical osteoporosis as they age. Some age-related osteopenia does appear to occur in both species, but the extent and significance of this is unclear. Laboratory studies indicate changes in calcium metabolism and bone characteristics with age in dogs similar to those seen in humans, and measures of bone density do show a negative association with age. Aged dogs also exhibit increased serum osteoprotegerin levels. This is associated with decreased bone density in humans, but its utility as a biomarker for osteoporosis and osteopenia is not conclusively established. There is negligible evidence concerning age-associated changes in bone structure and metabolism in companion cats. The decline in bone density in this species implies a possible shift in the balance of osteoblast and osteoclast

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**Figure 2**—Key mechanisms and manifestations of bone tissue aging. GH = Growth hormone. IGF-1 = Insulin-like growth factor-1. IL-6 = Interleukin-6. TNF-α = Tumor necrosis factor-α.
activity with age, but small studies using biomarkers of bone turnover have not revealed such a change with age after the period of rapid growth in young cats.65

Decline in bone mass in humans and laboratory animal models is driven, in part, by a loss of bone marrow stem cell capacity. Stem cells in the marrow shift with age from production of osteoblasts to production of adipocytes, leading to fat accumulation in the marrow and decreased osteogenesis. This alteration in stem cell behavior has been associated with age-related changes in activity of the sirtuin family of transcription factors and mTOR, both of which are important components of aging pathways in many different tissues.57

While dogs do exhibit decreased cellularity and increased adiposity of bone marrow with age, there are few data examining the number or function of bone marrow stem cells as a factor in canine bone aging. Some in vitro research does suggest that the proliferative and osteogenic capacity of canine bone marrow stem cells does decline with age.58 There is also little evidence concerning the characteristics of bone marrow and stem cell function changes with aging in cats.

GH is critical for maintenance of normal bone mass in humans, both directly and through effects mediated by IGF-1. Age-associated declines in the levels of GH and IGF-1 reduce both the production and function of osteoblasts. There is also a reduction in sensitivity to IGF-1 in aging bone, further reducing osteogenesis.59 Other age-related endocrine changes contribute to diminished bone mass and density, including declining levels of estrogen, which inhibit osteoclast activity, and of androgens, which are both directly anabolic and an indirect source of estrogen production via aromatization in males.59

The limited available evidence suggests that there are both similarities and differences in the role of endocrine mediators of bone growth and remodeling between dogs and other mammals. For example, GH and IGF-1 have anabolic effects on bone, and administration of GH or stimulation of GH production in old dogs can reduce osteolysis and stimulate osteogenesis.64 In contrast, dogs do not show the same extent of bone loss following ovariectomy as seen in humans and rodents, suggesting some differences in the relationship between sex hormones and the balance of bone production and remodeling.64

There is some evidence that GH and IGF-1 levels may decline with age in cats, although these studies involved few individuals within a limited age range. It is unclear whether these hormones play the same role in bone metabolism in cats as in other species. Therefore, the relationship between any age-related changes in these hormones and observed age-related changes in bone is uncertain. As in dogs, ovariectomy does not appear to lead to osteopenia in the cat.55

The role of inflammaging in age-related bone loss is an area of active investigation. While other factors have previously been considered more important, there is emerging evidence that the association between inflammaging and diminished bone density may reflect a causal relationship. IL-6, TNF-α, and other inflammatory cytokines promote osteoclast activity and interfere with osteoblast differentiation.64 The role, if any, of inflammation in canine bone aging has not been established, and as mentioned previously, it is unclear if dogs exhibit inflammaging.59 Similarly, while chronic inflammation may occur in older cats and be associated with morbidity, it is unknown if this process plays any role in age-related changes in bone.

The relationship between insulin metabolism and age-associated changes in bone mass and function is complex. Insulin exerts an anabolic effect on bone, reducing turnover and increasing bone density.65 However, it is well recognized that human diabetics have an increased risk of fracture despite relatively higher bone density than age-matched nondiabetic individuals.66 The leading hypothesis to explain this paradox is that insulin resistance and hyperinsulinemia lead to changes in bone microstructure than reduce strength despite preserved bone density.

Peripheral insulin resistance, associated with both aging and obesity, interferes with the anabolic effects of insulin, directly and mediated by IGF-1, on bone.66 Insulin resistance and hyperinsulinemia, due to aging or obesity, are also associated with chronic inflammation and changes in other metabolic signaling pathways that contribute to decreased bone mass and strength.66,67 Bone is also a metabolically active tissue, and there is a reciprocal relationship between bone metabolism and glucose metabolism that may lead to a vicious cycle of increasing insulin resistance and declining bone density.68

There is little direct evidence relating insulin metabolism and bone aging in dogs. Indirect evidence of some relationship comes from dietary restriction studies. Dietary restriction, predominantly caloric restriction, is one of the most consistently effective interventions for extending life span and health span in mammals. The proposed mechanistic explanations for the beneficial effects of caloric restriction include alterations in insulin metabolism as well as in IGF-1, sirtuin and mTOR activity, chronic inflammation, and other common aging pathways involved in the aging of many tissues.68

Caloric restriction studies in dogs have found improvements in life span and health span as well as concurrent alteration in some of these pathways, including improved insulin sensitivity and changes in IGF-1 levels.12 In one such study,12 an age-associated decline in bone density and mineral content was seen, and this appeared to be attenuated in dogs undergoing caloric restriction. While this suggests that insulin sensitivity and other aging pathways identified as salient in other species contribute to decreasing bone density in geriatric dogs, further research is clearly needed to establish specific causal relationships between common aging mechanisms and age-related changes in canine bone.

Insulin sensitivity may decline with age in cats,70 although the data are limited and may be confounded by age-associated changes in body weight and composition and other variables.72 There is no evidence

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addressing the impact of age-associated changes in insulin metabolism on bone composition or function.

Declining physical activity may play a role in age-associated bone loss in humans, although mechanical loading becomes less effective at stimulating osteogenesis with age.68 Physical activity can retard age-related bone loss and potentially stimulate improvements in bone density in the elderly, but there is controversy about the overall efficacy and the optimal type of activity.64

The impact of physical activity, and changes in activity levels with age, on bone density has not been examined in dogs, although improvements in bone density with exercise do occur in young dogs as in other young mammals.72,73 While immobilization has been shown to induce osteopenia in cats,71 no evidence exists to evaluate the role of physical activity on bone health and function with aging in companion cats.

**Aging changes in joints**

Changes in articular cartilage and joint structure and function with age are often similar to those seen in bone. An imbalance between catabolic and anabolic processes results in cartilage degradation.74 Decreased hydration and changes in structure and type of collagen molecules in articular cartilage also lead to increased rigidity and decreased tensile strength.77 These changes lead to an increased risk of OA, the most common age-associated disease of joint tissues.

The risk of OA is further increased by inflammaging. Inflammatory mediators, including C-reactive protein, IL-6, and TNF-α, increase the occurrence of chondrocyte senescence. Senescent chondrocytes not only fail to regenerate cartilage but also develop SASP, which includes further production of inflammatory cytokines and other cartilage-degrading substances.74 Senescent chondrocytes, like aged osteoblasts, are also resistant to anabolic signaling via IGF-1 and other mediators of cartilage production, further promoting cartilage loss. Local and systemic increases in inflammatory cytokines have been associated with development of OA in humans,75 and inflammaging is believed to be a key factor in the articular changes leading to OA.76

While the occurrence and severity of OA in humans is also related to other factors, such as body weight, genetic background, history of trauma, nutrition, etc, age-related change in cartilage and other joint components is arguably the most significant risk factor for this common and debilitating disease. The pathogenesis of age-associated OA, however, is complex and has not been completely elucidated. The evidence for the role of specific aging pathways, such as inflammaging, SASP, mitochondrial dysfunc-
tion, and others is very limited.74

Prevalence of OA increases with age in dogs, and age appears to be a major risk factor, along with body size, sex, neuter status, breed, and ontogenic factors.77 There is evidence for thinning and other changes in the structure and composition of cartilage with age, in both the presence and absence of OA, that are similar to those seen in other mammals.78 There also appear to be changes in patterns of expression of genes related to cartilage composition and degradation in dogs that resemble those seen in humans with OA, although the evidence is mostly from young dogs with hip dysplasia.79 Increases in some inflammatory cytokines, such as IL-6, in joint tissues associated with OA have been reported in dogs and resemble those seen in humans. However, this evidence often comes from young dogs with cranial cruciate ligament disease, which may not share the same pathogenesis as spontaneous age-associated OA, and the available data are very limited.74,79,80

As in dogs, OA is a common and clinical important pathology in older cats, and most research relevant to aging of joint tissues in this species concerns OA.35,81 Degradation of articular cartilage and increased localized inflammatory cytokine levels are features of OA in cats as in other species, although the pathogenesis of OA and the relative roles of aging and other variables are not well described.35,80 Chronic inflammation, associated with age and with age-related obesity, level of physical activity, changes in stem cell function, changes in nutrient sensing and the somatotrophic axis, and many other aging processes documented in other species have yet to be adequately studied in relation to the development of joint disease in elderly cats.

Physical activity has previously been considered a potential risk factor for age-associated degradation of cartilage and development of OA. However, it is becoming increasingly clear that in the absence of traumatic joint damage and significant congenital malalignment, physical activity actually retards age-associated degeneration of cartilage and the occurrence of OA in people.82,83

Some studies have suggested that increased physical activity may be a risk factor for development of OA in dogs.77 However, physical activity and joint loading alone are not likely to cause canine OA,84 so this risk may be related to type of exercise, timing of this exercise (eg, during periods of rapid growth), intensity of exercise, and the occurrence of trauma to joint tissues. Given the strong evidence in humans that physical activity can mitigate both potential risk factors for OA, such as obesity and sarcopenia, and may directly attenuate age-associated changes in cartilage that can lead to joint disease, further research is needed to clarify the role of exercise as a risk or protective factor with respect to aging changes in joints and OA in dogs.

The potential for confounding in studies of association between age and age-associated joint disease is high. Obesity, for example, is clearly a risk factor for OA.85 This is often explained in terms of increased loading of articular surfaces leading to cartilage damage and joint disease. However, studies involving long-term forced exercise in dogs carrying heavy weights do not show development of cartilage damage or other joint disease, suggesting that loading alone is not the critical factor.84 Obesity also contributes to a chronic inflammatory state in humans.86
(and possibly in dogs), and this may be a factor in the relationship between obesity and OA. The prevalence of both obesity and OA increases with age in dogs, and there may also be some age-associated increase in systemic inflammation. Caloric restriction in dogs reduces body weight, the occurrence of obesity, and the onset and prevalence of OA in dogs. Disentangling the causal relationships between these concurrent and interacting variables is difficult.

As is so often the case, there is little research directly evaluating the role of physical activity on the pathogenesis of OA in cats, or the interactions between this and other risk factors, such as inflammation and obesity.

**Brain tissue**

Similar to muscle tissue, the brain exhibits atrophy with aging, losing mass through cell death, which eventually leads to functional compromise (Figure 3). Both gray matter (cell bodies and unmyelinated axons) and white matter (myelinated axons) decline, and ventricular volume increases. This atrophy results from an imbalance between cell death and the maintenance and replacement of neurons. While many neurons in the adult brain are produced during early development and never replaced, the importance of neurogenesis in maintaining brain function is increasingly recognized. Decreased production of new neurons in some areas, such as the hippocampus, is a key driver of age-associated functional decline. As in other tissues, this decline in cell production is related to a decline in the proliferative capacity of relevant stem cells.

There has been extensive investigation of age-associated neurodegenerative disease in the dog, both because of the direct clinical impact of this on companion dogs and their owners and because of the relevance of canine brain aging as a model for Alzheimer’s disease and other age-related brain pathology in humans. Dogs clearly show patterns of white and gray matter atrophy and ventricular enlargement similar to those seen in humans. This involves loss and degeneration of neurons, and there is some evidence for impaired hippocampal neurogenesis in aging dogs.

Chronic inflammation is another common aging process that is involved in the loss of brain mass and function. Aberrant production of proinflammatory cytokines, including interleukin-1β (IL-1β), IL-6, and TNF-α, by microglia and astrocytes supports a neurotoxic milieu that contributes to neurodegeneration. These changes also interact with and contribute to dysregulated energy metabolism, including resistance to insulin and IGF-1 signaling and mitochondrial dysfunction, which further degrade neuronal homeostasis and function.

The role of cellular senescence and SASP in brain aging is just beginning to be elucidated. Replication-competent cells, such as astrocytes and glial cells, have been shown to exhibit signs of senescence and SASP in mammalian brains. There is also preliminary evidence that neurons may exhibit markers of senescence even though, as permanently postmitotic

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**Figure 3**—Key mechanisms and manifestations of brain tissue aging. IGF-1 = Insulin-like growth factor-1. IL-1β = Interleukin-1β. IL-6 = Interleukin-6. TNF-α = Tumor necrosis factor-α.
cells, they cannot be defined as senescent by the traditional criterion of irreversible cell-cycle arrest. More research is needed to clarify the role of cellular senescence in brain aging.

Interestingly, there are some signals of increased inflammatory activity and gene expression patterns in aging canine brain tissue, although the extent and importance of chronic inflammation for aging in this tissue is not clear. This is consistent with the general lack of information about the role of inflammaging in this species. Similar limited evidence is available concerning the role of mitochondrial dysfunction in canine brain aging, and there is negligible information regarding the role, if any, of cellular senescence and SASP in the aged canine brain.

Dysregulation of proteostasis and the accumulation of abnormal lipofuscin and protein aggregates is a common feature of brain aging. These are particularly important elements of age-associated brain diseases, such as Alzheimer’s disease (which involves accumulation of amyloid-β and tau proteins) and Parkinson’s disease (which involves cytoplasmic accumulation of α-synuclein). Accumulation of protein aggregates, including amyloid-β, tau, and lipofuscin are seen in aging canine brains. There are, though, some differences in the manifestation of this loss of proteostasis between dogs and humans. For example, although dogs do accumulate tau proteins, they do not show the same pattern of neurofibrillary tangles seen in humans with neurodegenerative disease.

Although the brain is not a mechanically active tissue in the way muscles, bones, and joints are, physical activity turns out to have significant beneficial effects on brain aging. Exercise appears to enhance neurogenesis and attenuate the age-related loss of brain mass in the hippocampus and globally. Through both direct effects in the brain and indirect effects on other tissues, physical activity can also reduce chronic inflammation, insulin resistance and metabolic dysregulation, and protein aggregation in brain tissue.

There is limited research available on the impact of physical activity on aging in canine brain tissue. Environmental enrichment and physical activity appear to preserve and improve cognitive function in aging dogs. It is hypothesized that this may involve preservation of neuronal mass and neurogenesis or attenuation of protein aggregation, but there is negligible experimental evidence connecting clinical impact and tissue effects.

Adipose tissue

Adipose tissue serves primarily as a storage depot for calories consumed in excess of current energy needs (Figure 4). However, adipose is also metabolically active, and it both manifests and

Figure 4—Key mechanisms and manifestations of adipose tissue aging. IL-6 = Interleukin-6. TNF-α = Tumor necrosis factor-α.
contributes to many of the physiologic changes associated with aging. While it is seldom considered as a tissue of clinical interest in aging dogs and cats, apart from the development of obesity, adipose plays a central role in the metabolic derangements of aging that lead to clinical problems in other tissues, such as the brain and the musculoskeletal system.

In humans, total body weight and body fat mass increase and lean body mass decreases with age. The distribution of adipose tissue also changes with age, shifting from subcutaneous to visceral adipose. This pattern is common but not universal among mammals. In dogs, total body fat mass increases with age, and there appears to be an increase in the ratio of visceral to subcutaneous fat. There is relatively little information on the impact of aging on adipose mass, distribution, and function in cats. In general, fat mass tends to increase with age in cats up to about 11 to 12 years, at which point both lean and fat mass often decline. One study has shown a relative increase in the body fat ratio without an increase in body condition score in older cats, suggesting a sarcopenic fat accumulation. However, the cats in this study were fed to prevent obesity, and although sarcopenic obesity is suspected to occur in cats, this has not been confirmed. A shift from subcutaneous to visceral adipose deposition occurs with obesity in cats, but it is unknown if this redistribution occurs in aging cats without obesity.

The age-associated redistribution of fat in humans impacts metabolism as visceral fat has a very different metabolomic profile from subcutaneous adipose. Increases in the proportion of visceral fat contribute to insulin resistance, dyslipidemia, and a chronic inflammatory state. These are all hallmarks of age-related metabolic dysfunction and risk factors for age-associated disease in humans. Similar changes in distribution in dogs and cats may have similar functional consequences, although the data are limited. Increased total and visceral fat mass is associated, for example, with insulin resistance in dogs. Sparse evidence also suggests that aging may also be associated with an increasing proinflammatory metabolite profile in canine adipose tissue. However, as mentioned previously, it is not yet clear the extent to which inflamming, driven by adipose or other tissues, actually occurs in the dog. There may be an increase in systemic inflammation with aging in cats, but this has not been explicitly linked to changes in adipose distribution or function.

The shift from subcutaneous to visceral adipose deposition in obese cats is associated with an increase in some biomarkers for systemic inflammation, but it is unknown if this relationship also pertains to aging cats without obesity. Obesity has been proposed as a model for the metabolic changes of aging since the two conditions share many physiologic features, so the changes in adipose distribution and function in obese cats may resemble those seen with aging in lean cats. However, obesity and aging are not identical in their mechanisms and effects, and cats also differ from humans and dogs in many aspects of their metabolic responses to obesity, so any extrapolation from the features of obesity to those of normal aging is tenuous.

In addition to increases in body fat and redistribution of fat mass associated directly with aging, the growing prevalence of obesity in aged humans, due to chronic positive calorie balance, exacerbates the inflamming and metabolic dysfunction seen in the elderly. Increasingly, elderly humans are affected by the concurrence of sarcopenia and obesity, particularly excessive visceral fat mass. This condition is identified as a clinical entity in its own right, sarcopenic obesity, because sarcopenia and obesity act synergistically to exacerbate metabolic dysfunction and increase morbidity and mortality risk by more than the sum of their independent health effects. This condition is associated with multiple age-associated morbidities in humans, including metabolic syndrome, insulin resistance, dyslipidemia, hypertension, and type 2 diabetes.

Obesity is certainly a growing problem in aging dogs, as in humans, and it is associated with similar metabolic dysfunction (eg, insulin resistance, dyslipidemia, increased inflammation) and increased morbidity and mortality. Both sarcopenia and obesity are age-associated conditions recognized in the dog, and the syndrome of sarcopenic obesity is believed to occur in the dog, but this syndrome has not been explicitly defined and evaluated in this species.

Similarly, obesity is a common condition in cats associated with various metabolic derangements and clinical disorders. However, cats appear to show a variable relationship between body mass and the relative proportion of lean and fat mass as they age that is different from that seen in dogs and humans. Some longitudinal studies show body weight increases from adulthood until roughly 12 years of age, predominantly due to increased fat mass with stable or slightly decreased lean mass. After this age, both fat and lean body mass decline, with a greater decline in fat mass, leading to a generalized underweight condition, rather than sarcopenic obesity.

As in other tissues, age-related changes in adipose include impaired capacity for proliferation and differentiation of adipose progenitor and stem cells. This leads to changes in distribution and function of mature adipose tissue and also to accumulation of senescent adipose cells. These cells, in turn, may exhibit SASP, contributing to inflamming in the organism through increased production of proinflammatory cytokines (eg, IL-6 and TNF-α) and decreased secretion of antiinflammatory adipokines (eg, adiponectin). Senescent adipocytes also exhibit decreased mitochondrial function.

It does appear that adipose stem cell function is impaired with aging in dogs and cats, as in humans, although further research is needed to elucidate the nature and extent of differences between adipose progenitor and stem cells in young and old animals of these species.
As with musculoskeletal tissues, physical activity has a significant influence on age-related changes in adipose tissue. Physical activity may also help preserve lean body mass, although this effect is weaker in the elderly compared with younger adults. Exercise may also attenuate the changes in distribution of adipose mass from the subcutaneous to the visceral compartment. Finally, physical activity improves mitochondrial function in adipose tissue, and it reduces markers of systemic inflammation, although it may do so directly more than through an effect on proinflammatory changes in adipose mass and function. Physical activity may help reduce obesity in dogs, and it appears to have some impact on the metabolism of adipose tissue, although whether it can significantly influence age-related changes in adipose mass, distribution, or function is unknown. Low levels of physical activity are a risk factor for obesity in cats, as is aging, but the impact of activity level on age-related patterns of change in adipose tissue mass, distribution, and function is unknown.

The web of tissue aging

This brief review of prominent aging changes in musculoskeletal, brain, and adipose tissues illustrates common processes associated with aging throughout the body, including declining stem-cell capacity, an imbalance between production and regeneration of tissue elements and the loss or senescence of stem cells, local and systemic inflammation, deranged nutrient sensing and energy metabolism, and impaired mitochondrial function. Ultimately, dysfunction at the level of each individual tissue affects other tissues and leads to clinical disease through diminished robustness and resilience of the organism. All of these mechanisms, and others not touched on, interact and reinforce one another in a complex web that ultimately leads to tissue dysfunction, disease, and death (Figure 5).

Adipose tissue, for example, demonstrates this self-reinforcing network quite clearly. The loss of stem cell function and development of SASP lead to local and systemic inflammation. This inflammation contributes to the loss of stem cell function because proinflammatory cytokines impair the differentiation of progenitor cells into preadipocytes, hinder the further differentiation and function of these preadipocytes, and promote adipocyte senescence. Age-associated adipose dysfunction also leads to ectopic lipid deposition in other tissues, such as liver, skeletal muscle, and bone marrow. This exacerbates insulin resistance, sarcopenia, and declining bone marrow stem cell function, further advancing the global process of aging-associated tissue dysfunction. Each tissue both experiences and contributes to the overall aging of the organism, reducing robustness and resilience and engendering the clinical manifestations of aging.

The specific aging phenotype that emerges in an individual animal is contingent on genetic, ontogenic, environmental, and stochastic factors, but the underlying physiologic processes are remarkably consistent between tissues, individuals, and even species. The goal of veterinary geroscience is to

![Figure 5](https://example.com/f5.png)

**Figure 5**—The web of tissue aging—a partial illustration of the interactions between key tissue-aging mechanisms. GH = Growth hormone. IGF-1 = Insulin-like growth factor-1.
understand these processes well enough to develop effective preventative and therapeutic interventions. A great deal of additional research is needed to clarify the details of aging mechanisms in dogs and cats. The relevance of specific cellular and molecular hallmarks of aging to the clinical phenotype of aging in cats and dogs, and the connections between these and physiologic mechanisms of aging at the tissue level, are areas ripe for further exploration. In light of the consistency seen across species in the core mechanisms of aging, the foundation already built in humans and laboratory animals provides a solid starting point for further research in dogs and cats. Clinical therapies to mitigate the negative health impact of aging on these species are a realistic long-term goal, and filling in the knowledge gaps highlighted in this review will pave the way to bringing such therapies into the hands of clinicians.

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References


