Influence of lifetime food restriction on causes, time, and predictors of death in dogs

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Objective—To describe effects of lifetime food restriction on causes of death and the association between body-mass characteristics and time of death in dogs.

Design—Paired-feeding study.

Animals—48 dogs from 7 litters.

Procedures—Dogs were paired, and 1 dog in each pair was fed 25% less food than its pair mate from 8 weeks of age until death. Numerous morphometric and physiologic measures were obtained at various intervals throughout life. Associations of feeding group to time and causes of death were evaluated, along with important associated factors such as body composition components and insulin-glucose responses.

Results—Median life span was significantly longer for the group that was fed 25% less food, whereas causes of death were generally similar between the 2 feeding groups. High body-fat mass and declining lean mass significantly predicted death 1 year prior to death, and lean body composition was associated with metabolic responses that appeared to be integrally involved in health and longevity.

Conclusions and Clinical Relevance—Results were similar to results of diet restriction studies in rodents and primates, reflecting delayed death from species- and strain-specific intrinsic causes. Clinicians should be aware that unplanned body mass changes during mid- and later life of dogs may indicate the need for thorough clinical evaluation. (*J Am Vet Med Assoc* 2005;226:225–231)

During the 20th century, a large body of research evolved toward understanding aging and how aging can be influenced in individuals and in populations. A considerable portion of this effort has focused on elucidating roles of nutrition, including nutrient requirements during senescence, complications and treatment of chronic diseases, and preventive strategies to delay chronic disease and death. The association among energy intake, energy utilization, and aging is particularly interesting in this respect. The most well-known intervention is long-term restricted food intake, which has a favorable influence on the life span of species as diverse as nematodes, spiders, rotifers, water fleas, fruit flies, fish, hamsters, mice, rats, and dogs.[1–3] Food restriction also modulates physiologic processes that may influence the expression of diseases that develop later in life. Results of studies[1–6] of rodents, dogs, and primates indicate that food restriction delays age-related death from species-, breed-, and strain-specific causes.

Evaluation of lifetime food restriction in a population of dogs offered the opportunity to assess characteristics and predictive aspects of intrinsic (nonenvironmental, arising from inside the body[7,8]) death in a large species that has a mean life span that lies intermediately between lower mammals, which have been studied extensively by use of food restriction models, and primates that presently are the subject of similar studies.[1,4–6] The purpose of the data reported here is to describe effects of lifetime food restriction on causes of death and associations among body composition and time of death in dogs. Overall life span data from this study have been previously reported.[2]

Materials and Methods

Dogs and housing—Forty-eight Labrador Retrievers from 7 litters were allocated to a paired-feeding study design.[9–11] Dogs were paired at 6 weeks of age by sex and body weight within litter and randomly allocated to either a control-fed or restricted-fed group. Dogs were housed in 2 × 19-m indoor-outdoor kennel runs with concrete floors. Free access to outdoors was available, and the activity level of the dogs was not restricted. All dogs were housed in the same environmental conditions for life, with no difference between feeding groups. Kennel assignment was maintained by original pairing, with either 2 (1 pair) or 4 (2 pairs) dogs/kennel. The study was approved by the supervising institutional animal care and use committee.

Diets and feeding regimens—Control-fed and restricted-fed dogs ate the same nutritionally complete and balanced noncommercial formula; only the quantity of diet provided was different between feeding groups.[9–11] Beginning at 8 weeks of age, each restricted-fed pair mate was fed a quantity equal to 75% of the amount of food that was consumed on the previous day by the respective control-fed pair mate. When the dogs were 3.25 years old, 2 adjustments were incorporated into the feeding protocol. All dogs were switched from a growth formula containing 27% protein to an adult formula containing 21% protein, and the amount of food given to the control-fed group (previously ad libitum-fed) was reduced and fed at a constant amount of 62.1 kcal of metabolizable energy/kg of ideal body weight to prevent insidious development of obesity. This procedure was similar to a protocol used for a study[12] of diet restriction in nonhuman primates. Restricted-fed pair mates continued to receive 75% of the consumption of corresponding control-fed pair mates. Details of experimental design and methods have been described.[9–11]

Animal health and monitoring—Dogs were monitored daily throughout life for signs of illness. Vaccinations against

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canine distemper virus, adenovirus type 1, canine parainfluenza virus, canine parvovirus, leptospirosis, *Bordetella bronchiseptica*, and rabies virus and preventive treatments for endoparasites were administered. Body weight, body composition, radiography of bones and joints, and numerous physiologic measurements were obtained at regular intervals throughout life as a part of the study design and to facilitate health monitoring. Most data were collected annually on the dogs' date of birth.

When necessary, appropriate therapeutic measures were instituted under veterinary supervision in a manner consistent with the management of the entire colony population. Similar disease conditions among dogs were managed as uniformly as medically possible. Diet and feeding group allocations were not changed because of illness, and choice of therapeutic measures for similar conditions was not influenced by feeding-group allocation. All dogs were sexually intact at the beginning of the study. However, if orchidectomy or ovariohysterectomy became necessary for purposes of treatment, the corresponding pair mate underwent the same procedure to maintain the experimental design.

Most (46/48) dogs ultimately were euthanatized for humane reasons. Eventual candidates for euthanasia were evaluated by research technicians and the attending veterinarian when quality of life was determined to be deteriorating to the point that further maintenance might not be appropriate. However, humane euthanasia was performed only after thorough diagnostic examination, careful monitoring and assessment of responses to treatment, serial evaluation of clinical condition, and consideration of prognosis, according to practices established for the entire colony. Similar procedures have been used previously in diet-restriction research with large mammals.[13]

Necropsy of all dogs was performed immediately after death. All tissues were inspected, and gross observations were recorded electronically during the procedure. Tissues harvested for histologic evaluation included 43 to 45 soft tissues (depending on sex and neutering status) and bone and diathrodial joints (hip, stifle, shoulder, and elbow joints). Tissues were sampled first in a uniform manner in accordance with the experimental protocol, and any visible lesions were sampled additionally. Tissues were preserved in neutral-buffered 10% formalin and were sectioned and stained by use of routine histologic techniques. The histopathologist was unaware of experimental group identification. Primary causes of death were determined by assessment of clinical, gross postmortem, and histopathologic outcome.

Body composition was assessed by **dual energy X-ray absorptiometry (DEXA)**,[a] which was performed annually near the date of birth, beginning at 6 years of age. All end-of-life DEXA analyses were performed prior to death. Data were evaluated longitudinally for associations with feeding group and death.

Statistical analyses—Statistical analyses of data incorporated the paired design of the study when possible. The difference in median life span between the 2 feeding groups was evaluated by use of the Wilcoxon signed rank test for matched pairs.[14] Annual percentage survival beginning at 7 years of age was compared by use of a continuity-adjusted, row-by-column χ^2 test.[15] The association between feeding group and cause of death was examined for each body system. The Cochran-Mantel-Haenszel test was used to examine differences between feeding groups in frequencies of causes of death in a paired analysis.[16] Differences in age at death (from failure of a given body system) between feeding groups and associations among body composition data with survival were evaluated by use of Cox proportional hazards regression models.[17] These models examined the impact of covariates on hazard of death. In this context, hazard was the instantaneous risk of death in an individual dog that had reached a given age. Because there were multiple causes of death, when examining a particular cause of death (categorized by body system), all deaths from other causes were censored at the time of death.[18] When examining survival with Cox proportional hazards regression models, the data were too sparse to stratify by pairs; therefore, stratification by litter was used. The difference in mean age at death between dogs in each group that died because of neoplasms was evaluated by use of a 2-tailed *t* test. For all analyses, values of $P < 0.05$ were considered significant.

Results

The median life span was 11.2 years for control-fed dogs, which was significantly ($P < 0.01$) less than the median life span of 13.0 years for restricted-fed dogs.[2] Beginning from 11.5 years of age, percentage survival differed significantly ($P < 0.05$) between the 2 groups until 14 years of age, when 2 dogs in the restricted-fed group were the last surviving dogs on study (**Table 1**). Nine restricted-fed dogs were alive after all control-fed dogs had died.

Primary causes leading to death or euthanasia were most frequent in the musculoskeletal (n = 26) and gastrointestinal (12) systems (**Table 2**). Ten primary causes of death were not classified into one of these categories. Neoplastic diseases within the musculoskeletal and gastrointestinal systems (n = 4) and other body systems (7) caused 11 deaths.

All musculoskeletal diseases resulted in deaths at a mean age of 10.6 years among 14 control-fed dogs. Osteoarthritis of diarthrodial joints was the primary cause of musculoskeletal disease at a mean age of 11.5 years among 11 of those 14 dogs. There were single occurrences of complicated spondylosis of the lumbosacral portion of the vertebral column, bone neoplasm, and fibrocartilaginous embolism of the spinal cord.

All musculoskeletal diseases resulted in death at a mean age of 13.1 years among 12 restricted-fed dogs. Osteoarthritis of diarthrodial joints (7 dogs; mean age, 13.1 years) and complications of severe spondylosis of the lumbosacral portion of the vertebral column (4 dogs; mean age 13.1 years) developed most frequently. There was a single occurrence of severe intervertebral

Table 1—Comparison of annual survival status beginning at 7 years of age among dogs fed a complete and balanced diet (control-fed [n = 24]) and a group of siblings fed 75% of the same diet (restricted-fed [24]).

Year	Percentage alive Restricted-fed	Percentage alive Control-fed	*P* value*
7.0	91.67	95.83	1.0000
8.0	87.50	87.50	1.0000
9.0	87.50	87.50	1.0000
10.0	87.50	75.00	0.4595
11.0	75.00	54.17	0.2274
11.5	75.00	41.67	0.0404
12.0	70.83	29.17	0.0094
13.0	50.00	4.17	0.0012
14.0	8.33	0.00	0.4701

*Continuity-adjusted χ^2 test.

Table 2—Causes of death among dogs fed a complete and balanced diet (control-fed [n = 24]) and a group of siblings fed 75% of the same diet (restricted-fed [24]).

	Restricted-fed			Control-fed		
Pair No.	Age (y)	Sex	Cause of death	Age (y)	Sex	Cause of death
Litter 1						
1	13.97	M	Osteoarthritis, elbow joints	10.80	M	Chronic liver disease
2	14.56	F	Chronic liver disease	10.94	F	Chronic liver disease
3	6.29	F	Megaesophagus	11.61	F	Chronic liver disease
Litter 2						
4	13.57	M	Osteoarthritis, multiple joints	12.68	M	Fibrosarcoma, spermatic cord
5	12.38	F	Osteoarthritis, multiple joints	9.50	F	Chemodectoma
6	13.50	F	Pancreatic acinar carcinoma	12.84	F	Osteoarthritis, multiple joints
7	13.17	F	Gastroesophageal leiomyoma	11.14	F	Diabetes mellitus
Litter 3						
8	14.11	F	Osteoarthritis, multiple joints	12.94	F	Osteoarthritis, multiple joints
Litter 4						
9	12.46	M	Chronic liver disease	9.66	M	Osteoarthritis, hip joints
10	12.77	M	Lumbosacral vertebral disease	12.35	M	Osteoarthritis, multiple joints
11	4.30	F	Infarction ileum	3.50	F	Squamous cell carcinoma, maxilla
12	13.00	F	Lumbosacral vertebral disease	12.41	F	Mammary adenocarcinoma
Litter 5						
13	13.31	M	Lumbosacral vertebral disease	9.14	M	Lymphosarcoma, alimentary
14	12.84	M	Aspiration pneumonia	10.00	M	Osteoarthritis, hip joints
15	13.51	F	Lumbosacral vertebral disease	11.37	F	Osteoarthritis, hip joints
16	10.68	F	Chronic fibrosing pneumonitis	10.86	F	Hemangiosarcoma
Litter 6						
17	10.24	M	Lymphosarcoma, multicentric	11.18	M	Chronic liver disease
18	13.69	M	Osteoarthritis, multiple joints	12.93	M	Osteoarthritis, multiple joints
19	13.29	F	Mammary tubular carcinoma	13.29	F	Osteoarthritis, multiple joints
Litter 7						
20	13.40	M	Osteoarthritis, multiple joints	11.50	M	Osteoarthritis, multiple joints
21	12.90	F	Vertebral disk disease	10.85	F	Lumbosacral vertebral disease
22	7.92	F	Mammary adenocarcinoma	7.69	F	Osteoarthritis, hip joints
23	11.85	F	Gastric rupture	11.99	F	Osteoarthritis, multiple joints
24	10.72	F	Osteoarthritis, hip joints	7.27	F	Spinal fibrocartilagenous embolism

disk disease. Restricted feeding resulted in a lower (P = 0.002) hazard of death from a musculoskeletal cause, indicating that death from generally similar diseases occurred at different times between the 2 feeding groups.

Death was associated with diseases of the gastrointestinal system (esophagus, liver, pancreas, stomach, and intestinal tract) in 7 restricted-fed and 5 control-fed dogs; mean ages at death were 10.9 and 10.7 years, respectively. Chronic-active liver disease caused death in 2 restricted-fed (mean age, 13.5 years) and 4 control-fed (mean age, 11.1 years) dogs. One death in each feeding group was caused by malignant disease involving the gastrointestinal system. Nonmalignant gastrointestinal (esophagus, stomach, and intestinal tract) diseases resulted in 4 deaths among restricted-fed dogs (mean age, 8.7 years) and no deaths among control-fed dogs. Feeding groups were similar ($P > 0.05$) in hazard of death from causes involving the gastrointestinal system.

Eleven dogs died or were euthanatized because of neoplastic diseases of musculoskeletal, gastrointestinal, or other body systems. Included were 5 restricted-fed (mean age, 11.6 years) and 6 control-fed dogs (mean age, 9.7 years). The neoplasms were diverse by type and location in both groups and included 4 sarcomas, 6 carcinomas, and 1 benign tumor. These observations were not analyzed by competing risks methodology due to the requirement for mutually exclusive body systems.[17] Although mean ages at death from neoplasms in the 2 groups were nearly 2 years apart, a t test analysis did not reveal differences between groups ($P > 0.05$). The analysis was complicated, however, by small sample sizes and a wide age range among dogs that died because of neoplastic processes.

Among restricted-fed dogs, death was associated with respiratory disease in 2 siblings, whereas death was not associated with respiratory disease among control-fed dogs. Neoplasms of the reproductive and hematopoietic systems were associated with death in 4 and 3 dogs, respectively. Death was associated with the endocrine system in 1 female control-fed dog with diabetes mellitus, which was the only occurrence of diabetes mellitus among the study population. Because the number of deaths associated with respiratory, reproductive, hematopoietic, and endocrine causes was small, statistical evaluations of differences in incidence and life span between feeding groups were not performed for these outcomes.

Evaluation of the association between body-mass components and death revealed that relative amounts (percentages) of lean and fat mass 1 year before death were highly predictive ($P < 0.002$) in an expected inverse manner. A high percentage of fat mass predicted death, and a high percentage of lean mass predicted a protective effect from death. Evaluation of absolute

Table 3—Predictive associations among body mass components and survival time among dogs fed a complete and balanced diet (n = 24) and a group of siblings fed 75% of the same diet (24).

		Z values from Cox regression models*			
Time to Death	**Tissue**	**Relative (%)**	**Gain/loss**	**Absolute (g)**	**Gain/loss**
0 time**	Bone	–2.11	NA	–0.17	NA
	Fat	2.20	NA	2.08	NA
	Lean	–2.19	NA	–0.37	NA
1 year	Bone	–1.89	0.73	0.82	–1.79
	Fat	3.24	–1.23	3.45	–0.95
	Lean	–3.22	1.21	0.99	–3.04
2 years	Bone	–1.23	–0.74	0.75	0.52
	Fat	2.14	0.96	2.41	1.26
	Lean	–2.10	–0.99	1.59	0.81

*Z = 1.96 corresponds to a P value of 0.05. Z = 3.00 corresponds to a P value of 0.0027. Z = 3.29 is the cutoff for significance (P = 0.001).
**0 time = Time of death. 1 year = 1 year before death. 2 years = 2 years before death.
NA = Not applicable.

weights of body-mass components indicated that high body fat (in grams) predicted ($P < 0.001$) death, again most strongly 1 year before death, whereas declining grams of lean body mass predicted ($P < 0.002$) death most strongly during the same period (**Table 3**).

Discussion

Data that were previously reported from this study indicated that restricted-fed dogs had a longer median life span (by 1.8 years) than control-fed dogs.[2] Restricted-fed dogs also weighed less; had less body fat; and had lower concentrations of triglycerides, triiodothyronine, insulin, and glucose in serum after food was withheld, compared with control-fed dogs. Results of IV glucose tolerance tests performed annually in control-fed and restricted-fed dogs at 9 through 12 years of age indicated that restricted-fed dogs had lower peak serum glucose concentrations and delta G (increase from baseline to peak glucose concentration).[2] The time for serum glucose concentrations to return to baseline and rate of return to baseline were faster among restricted-fed dogs.[2] These observations are consistent with results of food-restriction studies performed in other mammals.[3–6,19–21]

Exploration of longevity by use of continuity-adjusted χ^2 analysis indicated longer survival times among restricted-fed dogs from 11.5 until 14.0 years of age, when all control-fed dogs had died and < 10% of the dogs in the restricted-fed group remained alive. These data suggest that failure to detect different maximum survival times between the 2 feeding groups likely resulted from the size of the study population.

Diseases that led to death and body systems that were affected were generally similar in both groups of dogs. Principally, time of death differed between the 2 groups. Other breeds of dogs that were housed contemporaneously in the same facility had differing patterns of mortality; therefore, sharing of environmental influence alone does not explain the death patterns observed among the study population. Interestingly, results of a genetic study[22] in humans indicated that there was no evidence that longevity was influenced by shared environmental (family) experience.

Analysis of data reported previously from this study[11] indicated that radiographic evidence of osteoarthritis of multiple diarthrodial joints was more frequent among control-fed dogs (77%) by 8 years of age, compared with calorie-restricted dogs (10%). Restricted-fed dogs also had a lower hazard of death from all musculoskeletal causes. Restricted-fed dogs had a higher frequency of vertebral column disorders as causes of death later in life, compared with control-fed dogs. This difference could have been partly attributable to the longer median life span detected among restricted-fed dogs, permitting more time for vertebral column disorders to develop at advanced ages in susceptible dogs. Alternatively, dogs that have normal or near-normal hip joints may transmit greater loads through the caudal portion of the vertebral column than dogs with severe osteoarthritis of the hip joints, possibly reflecting differences in weight bearing that could facilitate development of vertebral column disease in susceptible dogs. The clinical signs of osteoarthritis of the hip joint and diseases of the caudal lumbar portion of the vertebral column can be similar[23]; however, 4 of the 5 dogs that eventually were euthanized because of diseases of the vertebral column had only mild radiographic changes in the hip joints, even during advanced age.

Eight dogs in the study (involving both feeding groups) died because of liver disease or malignant neoplasms of digestive tract organs. Nonmalignant diseases that affected the esophagus, stomach, or intestines caused death only in restricted-fed dogs (n = 4); however, the disease was different in each of these 4 dogs and each dog was from a different litter. The small number of dogs precluded additional statistical analyses, and the various diagnoses and litters of origin did not facilitate further qualitative interpretation. The same was true for the small number of causes of death that affected other body systems.

Evaluation of neoplastic diseases has been an important component of many nutritional studies involving rodent strains in which death from specific types of tumors typically occurs at a high frequency. In our study, an array of malignancies was observed among causes of death, affecting overall a similar number of dogs in each feeding group. Survival analysis was performed after categorizing causes of death according to body system, and neoplasms did not qualify for this analysis. The neoplasms that caused death were distributed over several body systems as primary or metastatic events (involving 23% of the dogs) with

wide age variance. Therefore, the ability to detect differences statistically in tumor-associated death was limited. Nonetheless, the mean age at death of restricted-fed dogs because of tumors was nearly 2 years later than control-fed dogs.

Lymphosarcoma, hemangiosarcoma, and carcinoma of glandular or ductal elements of mammary tissue are malignancies that develop frequently in dogs.[24–26] Malignant chemodectoma and pancreatic acinar carcinoma develop less frequently and usually are advanced by the time of diagnosis.[27,28] Gastroesophageal leiomyoma seems to develop infrequently and tends to develop in old dogs,[29] as was detected in our study. Maxillary squamous cell carcinoma in a 3-year-old dog and fibrosarcoma involving the spermatic cord and peritoneum appear to be uncommon in dogs and therefore may be unexpected in a population of 48 dogs.

A variety of species- and strain-related physiologic and pathologic outcomes of aging have been influenced by diet restriction in models that have used rodents in different experimental and environmental settings. Pathologic outcomes that have been delayed by diet restriction in rodents include nephropathies[30–33]; gastric ulcer[30]; cardiomyopathies and hypertension-related lesions[30–32,34]; osteodystrophy[35]; autoimmune renal disease[36]; cataracts[37]; degeneration of the neural retina[38]; and a number of neoplasms including mammary and lung tumors, leukemias, lymphoma, pituitary adenoma, and pancreatic adenoma.[39–45] On the other hand, urinary bladder papilloma, fibroma, fibrosarcoma, various carcinomas, and some endocrine tumors were either unaffected by diet restriction or expressed with increased frequency.[46]

Most studies of restricted feeding of primates are in progress. However, a summary[4] of early reports from these studies and results of a study[13] in control-fed and diet-restricted rhesus monkeys indicate that species-specific problems such as obesity, diabetes mellitus, and hypertension also are likely to be delayed or prevented.

The fact that phenotypes of aging and intrinsically mediated death differ among and within species likely reflects, at least in part, the way that genes are expressed.[22,47–49] In our study, body systems affected by causes of death and some of the specific causes of death were similar in the 2 groups of dogs, which supports the concept that genetic constitution plays an important role in the nature of intrinsically mediated death. Furthermore, the difference between the 2 groups in median life span suggests that modulators such as diet restriction act in part by influencing factors such as the timing of pathologic events or the risk for occurrence. The favorable response to diet restriction across species, with respect to longevity and many species- and strain-specific diseases, underscores the robust effect of feeding programs that restrict energy intake.[1–3]

In our study, body composition characteristics of dogs were associated with their outcome, but whether declining lean mass and increased fat mass (and their metabolic cause-effect relationships) are predictive through similar or dissimilar underlying mechanisms is not presently understood. Declining lean mass was predictive of death, most significantly at a year prior to death. Observations of body composition also have been reported from late-life studies of rodents. When inert gas uptake was used to make repeated measurements of total body fat and fat-free mass, individual male Sprague-Dawley rats maintained stability of fat-free body mass into senescence.[50] Results of a life span study[51] of male Sprague-Dawley rats, in which investigators examined the association between body water components and fat-free mass, indicated that stability was maintained into advanced age. Results of a life span study[52] of diet restriction in male Fischer-344 rats indicated that there was no progressive decline of lean body mass with advancing age, but decline of lean mass was observed after the onset of terminal disease in the population. The longer advance prediction of death by the observed loss of lean body mass in dogs, compared with rodents, may represent species differences associated with the shorter life span of rodents or may reflect other physiologic factors.

In elderly humans, precipitous unintentional weight loss is consistently associated with terminal outcome,[53,54] although some confusion in related literature arises from the difficulty of precisely defining and comparing human populations that have been studied.[55] Nevertheless, an independent association with death[54,55] suggests that rapid loss of weight late in life may not simply indicate the presence of chronic disease.[55] Considered together, results of these studies among species imply that rapid loss of body mass late in life, particularly lean body mass, may predict death independent of specific causes. Although specific underlying genetic and metabolic mechanisms are not entirely understood, major contributing factors to loss of lean mass and resultant disability during aging (and during preterminal conditions) may include loss of skeletal muscle fibers secondary to loss of motor neurons, reduced activity, altered endocrine status, anorexia and consequent reduced protein intake, reduced protein synthesis, and increased production of inflammatory mediators.[56]

In our study, persistently high fat mass also predicted death among dogs. Evaluation of the association between body fat with insulin-glucose metabolism in humans and primates suggests a threshold effect for insulin resistance at about 22% (primates) to 28% (humans) fat mass.[57,58] This association may have an age-related component in humans.[59] Data from an earlier report of our study[60] indicate that body-fat mass and insulin resistance also were correlated; the data reflected a threshold for increased insulin resistance above approximately 5,000 g of body fat (20% to 25% fat among these Labrador retriever dogs), which approximates the threshold range that has been reported for primates and humans.[57,58] However, some species differences in details of related metabolic processes may exist. For example, excessive abdominal fat depot in primates and humans was associated with hyperinsulinemia and glucose intolerance.[61–63] In dogs, the abdominal fat depot (as percentage of total tissue) and the total body-fat mass were similarly correlated with the glucose tolerance variables basal and peak insulin, change in insulin from basal to peak, time for glucose return to baseline, insulin sensitivity, and late-phase

insulin secretion.[60] These observations suggest that the abdominal fat depot may be of less independent metabolic importance in dogs.

Lower insulin sensitivity is considered to be an early indicator of defective energy regulation.[64] Hyperglycemia and hyperinsulinemia have been associated with cellular dysfunction and chronic disease,[60,65–68] and it has been proposed that lower glucose and insulin production may partially explain the delayed senescence that is frequently observed during diet restriction protocols.[69] Greater insulin sensitivity is associated with reduced hazard for chronic disease in diet-restricted dogs.[60] Results of another study[13] indicated that diet-restricted primates had a 2.6-fold lower risk of death, compared with control-fed primates. In that study,[13] hyperinsulinemia in obese control-fed monkeys was associated with a 3.7-fold higher risk of death.[13] Similar associations among insulin resistance and hyperinsulinemia, obesity, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and neoplasia have been detected.[70] Interestingly, however, the basal serum glucose of diet-restricted dogs decreased with advancing age to a greater extent than was observed among control-fed dogs. Simultaneously, basal insulin concentrations tended to increase, creating insulin-glucose associations that may be unique in aging dogs.[2]

In our study, optimal lean and fat body composition were associated with metabolic responses that appeared to be integrally involved in health and longevity.[60] In light of similar findings among numerous species and strains of vertebrate and invertebrate animals, it should not be unexpected that food-restricted dogs would have similarly delayed death from species- or breed-related causes. However, this should not define an obligate expectation that every species or strain or cause of intrinsically mediated death will be affected uniformly and universally by calorie restriction and likewise should not suggest that causes of death in populations will necessarily establish uniform or dysuniform patterns. Within populations, individuals respond differently to the same pressures, a likely result of genetic heterogeneity that predisposes toward early death for some and longer survival for others, with varying causality.[7]

Results of studies[22,71] of humans and *Drosophila* populations indicate that longevity is moderately heritable in a quantitative manner, and it has been suggested that gene-environment interactions indirectly influence longevity in important ways.[22] Whether or how the fundamental effects of long-term energy restriction and their downstream metabolic influences may involve such interactions remains to be established firmly. Despite the complexity of these questions, energy restriction is well documented within and across species as a successful interventional influence on species-and population-based life span.

a. Model DPX alpha dual energy x-ray absorptiometer, Lunar Corp, Madison, Wis.

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