ORIGINAL RESEARCH

Effects of Age on Inflammatory Profiles and Nutrition/Energy Metabolism in Domestic Cats

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Background: Animals tend to increase in body weight and body condition score (BCS) with aging. Serum diagnostic markers related to energy metabolism may show changes even in healthy cats with aging.

Materials and Methods: Seventy domestic cats were recruited for this study. Based upon the modified AAFP-AAHA Feline Life Stage Guidelines, animals were divided into six groups: Junior (7 months–2 years), Prime (3 −6 years), Mature (7–10 years), Senior (11–14 years), Geriatric-obese (15 years ≤) and Geriatric-thin (15 years ≤). Their body condition scores (BCS) ranged from 3/9 to 9/9. Changes in metabolites, inflammatory markers, hormone concentrations and enzyme activities related to energy metabolism were investigated in serum of 70 domestic cats of various ages.

Results: Serum glucose (GLU) concentrations in the Mature, Senior, and Geriatric-obese groups were significantly higher than those in the Junior group. Serum amyloid A (SAA) concentrations in the Geriatric-thin group were significantly increased compared with the Junior group. SAA concentrations in the Geriatric-obese group tended to increase although there were no statistically significant differences. In the Mature, Senior, Geriatric-obese and Geriatric-thin groups, malate dehydrogenase/lactate dehydrogenase (M/L) ratio, an energy metabolic indicator, tended to decrease compared with the Junior group. In the Senior group, triglyceride (TG) concentrations were significantly increased compared with the Junior group. In the Geriatric-obese and Geriatric-thin groups, blood urea nitrogen (BUN) concentrations were significantly increased compared with the Junior group. In the Geriatric-obese group, albumin (ALB) concentrations were decreased compared with the Junior group.

Conclusion: Aged domestic cats tend to increase in body weight and BCS. In addition, serum GLU, TG, SAA, and BUN concentrations increased and serum ALB concentrations and M/L ratio decreased. These diagnostic markers may be useful to detect small changes related to energy metabolism with aging that may cause obesity with light inflammation in healthy cats.

Keywords: aging, domestic cats, M/L ratio, obesity, SAA

Introduction

In humans, physical activities decrease with aging and body mass index (BMI) and fat distribution change.[1,2] Energy metabolism is downregulated in aged humans and excess calories are prone to be accumulated as ectopic fat in the abdominal cavity. Aged mice exhibited altered nutrient handling (glucose intolerance, insulin resistance, reduced fatty acid oxidation, and reduced ketogenesis), decreased mitochondrial biogenesis, oxidative phosphorylation, expression of stress defense genes, and apoptosis regulation.[3] Obesity is an excessive accumulation of triglyceride in adipose tissues, due to an energy imbalance where energy intake exceeds energy expenditure. Prevalence of obesity has

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increased rapidly in recent years in humans, with aging and obesity associated with various metabolic abnormalities that can lead to cardiovascular morbidity and mortality.[4] Metabolic syndrome has been related to the increasing prevalence of obesity, which is escalating among older age groups.[5]

Cats are more prone to become obese compared with dogs due to their unique characteristics in glucose and lipid metabolism such as a lack of hepatic glucokinase activities and low insulin signaling activities.[6,7] Cats are also prone to be insulin resistant compared with dogs due to low mRNA expression of insulin receptor substrate-1 (IRS-1), insulin receptor substrate-2 (IRS-2), and phosphatidylinositol 3-kinase (PI3-K) P-85 in insulin-responsive tissues (liver, skeletal muscle, abdominal fat, white blood cells).[8] In cats, the prevalence of obesity has increased with aging in recent decades as it has in humans.[9,10] However, alteration in energy metabolism with aging in cats is not well investigated.

In this study, we investigated changes in serum metabolites, hormone concentrations and enzyme activities as diagnostic markers for energy metabolism in healthy cats of various ages. Changes in these reference values of healthy cats with aging seem to be useful to understand onset mechanisms of aging-related disorders, including obesity. The aim of this study is to investigate changes in serum diagnostic markers associated with energy metabolism in healthy cats with aging.

Materials and Methods
Animals
Seventy domestic cats having a medical examination at a veterinary clinic in Tokyo from October 1 to December 5, 2018 were recruited. Written informed consent was obtained from each client. Based upon modified AAFP-AAHA Feline

Life Stage Guidelines,[11] animals were divided into six groups: Junior (7 months–2 years), Prime (3−6 years), Mature (7–10 years), Senior (11–14 years), Geriatric-obese (15 years <) and Geriatric-thin (15 years <) (Table 1). Breeds of Mix, Scottish Fold, Munchkin, Japanese Cat, American Shorthair, Ragdoll, Selkirk Rex, Norweigian Forest Cat, and Persian were included (Table 1). Eight cats with clinical symptoms were investigated to evaluate serum SAA concentrations compared with those in healthy cats (Table 3). Ethical approval for this study was obtained from Nippon Veterinary and Life Science University (27S-1). We confirm this study was conducted following best veterinary practice procedures.

Body Weight (BW) and Body Conditioning Score (BCS) Measurement
Body weight (BW) was measured at the health checkup. In Japan, body condition scores (BCS) of cats are usually examined with a 5-point system. However, this system is vague. To evaluate in detail, we employed a 9-point system: 1/9, emaciated; 2/9, very thin; 3/9, thin; 4/9, underweight; 5/9, ideal; 6/9, overweight; 7/9, heavy; 8/9; obese; 9/9, severely obese).[12] In the Geriatric groups, ≅4 of BCS was classified as the Geriatric-thin group while ≅6 of BCS was classified as the Geriatric-obese group in this study.

Blood Sampling and Analysis
Fasting blood samples at least 8 h after last meal were taken from jugular veins of cats. Serum was recovered by centrifugation at 3000 g, for 5 min at 4°C and stored at −80°C until use. GLU, TG, total protein (TP), BUN, creatinine (CRE) and ALB concentrations and alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP) activities

Table 1 Profile of the Age, Breed and Gender of 70 Cats in This Study

Breed	Junior	Prime	Mature	Senior	Geriatric-Obese	Geriatric-Thin	Total
Age (range)	7 months-2 years	3–6 years	7–10 years	11–14 years	>15 years	>15 years	
Mix	11	8	11	10	2	3	45
Scottish Fold	3	4	1	0	0	0	8
Munchkin	1	1	3	0	0	0	5
Japanese Cat	0	0	1	2	1	0	4
American Shorthair	0	0	3	0	0	0	3
Ragdoll	1	0	1	0	0	0	2
Selkirk Rex	0	1	0	0	0	0	1
Norwegian Forest Cat	0	0	0	1	0	0	1
Persian	0	0	0	1	0	0	1
Total	16	14	20	14	3	3	70

were measured using an auto analyzer (JCA-BM2250, JEOL Ltd, Tokyo, Japan) with the manufacturer's reagents at FUJIFILM Monolith Co., Ltd (Tokyo, Japan). Serum lactate dehydrogenase (LDH)[13] and malate dehydrogenase (MDH)[14] activities were measured by previously described methods. The serum MDH/LDH (M/L) ratio was calculated as MDH activities divided by LDH activities. Serum adiponectin (ADN) concentrations were measured with commercial ELISA kits, mouse/rat adiponectin ELISA kit (Otsuka Pharmaceutical Co., Ltd, Tokyo, Japan). Ten thousand-fold diluted serum was applied for ADN measurement. Acceptable detection range was estimated as from 0.25 ng/mL to 8.0 ng/mL by calibration curve[15] Serum amyloid A (SAA) concentrations were measured with commercial ELISA kit (CAT SERUM AMYLOID A (SAA) ELISA, Life Diagnostics, Inc., West Chester, USA). Denatured (at 60°C, for 1 h) serum was diluted at least 50-fold for SAA measurement according to the instructions. Acceptable detection range was estimated to be 0.94 ng/mL to 15 ng/mL[16] by calibration curve.

Statistical Analysis

Results are presented as means ± standard deviation (SD). Statistical significance was determined by One-way ANOVA. The significance level was set at $P < 0.05$ or $P < 0.01$. Correlation coefficients and P values between the age and examined parameters were calculated by a multivariable regression analysis. Significance levels were set at $P < 0.05$ or $P < 0.01$. Correlation coefficients were evaluated as follows: |0.7–1.0|: excellent, |0.4–0.7|: moderate, |0.2–0.4|: weak, | 0–0.2|: no correlation.

Results
Changes in Body Condition Score (BCS)

As shown in Table 2, BCSs in Junior (7 months to 2 years), Prime (3–6 years), Mature (7–10 years), Senior (11–14 years), Geriatric-obese (15 years <), and Geriatric-thin (15 years <) groups were 5.7 ± 0.8, 5.6 ± 0.8, 6.6 ± 1.3, 6.6 ± 1.6, 5.3 ± 0.5, and 3.7 ± 0.5 respectively. In Junior group, 3 of 16 (18.8%) cats were ≧ 7/9 of BCS. In Prime group, 3 of 14 (21.4%) cats were ≧ 7/9 of BCS. In Mature group, 10 (50.0%) of 20 cats were ≧ 7/9 of BCS. In Senior group, 7 (50.0%) of 14 cats were ≧ 7/9 of BCS. Three (50.0%) of 6 geriatric group cats were ≧ 6/9 of BCS while 3 (50.0%) of 6 cats were ≧4/9 of BCS.

Table 2 Changes in Biomarkers Among Different Ages in 70 Cats

	Junior (16)	Prime (14)	Mature (20)	Senior (14)	Geriatric-Obese (3)	Geriatric-Thin (3)
Age (range)	7month to 2 years	3 years to 6 years	7 years to 10 years	11 years to 14 years	15 years <	15 years <
Age (Av)	1.9±0.6	4.6±1.1	9.0±1.3	12.1±0.9	15.9±0.5	16.6±0.3
Weight (kg)	4.3±0.7	4.2±0.9	5.0±1.4	4.9±1.3	4.2±0.9	3.3±0.4
BCS	5.7±0.8	5.6±0.8	6.6±1.3*	6.6±1.6*	6.3±0.5	3.7±0.5**
GLU (mg 100mL^{-1})	103.9±20.3	107.7±24.7	139.1±48.4*	137.7±29.5**	150.3±58.2*	128.3±22.0
AST (IU L^{-1})	28.1±13.7	27.8±5.7	25.9±7.7	25.8±8.4	27.3±3.3	21.3±4.2
ALT (IU L^{-1})	66.5±65.1	52.9±15.0	47.6±22.1	47.9±28.7	36.3±5.7	34.7±6.6
TG (mg 100mL^{-1})	44.2±32.1	37.5±26.0	59.8±65.3	137.5±146.3*	28.7±5.9	27.7±9.5
SAA (ng mL^{-1})	28.2±54.3	22.4±34.4	57.1±119.3	83.4±163.1	103.4±116.2	215.1±155.7*
ADN (µg mL^{-1})	5.9±4.1	5.2±3.8	4.7±2.7	3.8±4.2	7.3±1.4	5.0±1.1
LDH (IU L^{-1})	79.6±33.4	54.3±35.2	49.5±26.1**	62.2±39.6	42.5±18.9	31.4±9.8*
MDH (IU L^{-1})	39.3±67.1	20.9±26.0	8.6±4.8	21.0±39.7	9.3±6.0	6.9±2.4
M/L	0.470±0.678	0.496±0.614	0.226±0.179	0.293±0.300	0.343±0.282	0.272±0.172
TP (g 100mL^{-1})	7.4±0.9	7.5±0.4	7.6±0.6	7.6±0.5	7.2±0.0	7.4±0.2
ALB (g 100mL^{-1})	3.4±0.3	3.4±0.3	3.3±0.3	3.3±0.3	2.9±0.1*	3.2±0.0
ALP (IU L^{-1})	116.3±51.8	81.6±39.2	87.4±23.7*	81.6±26.5*	69.0±11.4	95.3±52.2
γ-GPT (IU L^{-1})	0.2±0.2	0.2±0.1	0.3±0.2	0.2±0.2	0.2±0.1	0.3±0.1
BUN (mg 100mL^{-1})	26.1±4.2	26.0±4.1	26.1±5.1	27.5±5.0	57.7±30.1**	31.7±2.1*
CRE (mg 100mL^{-1})	1.5±0.4	1.5±0.3	1.5±0.3	1.4±0.2	2.4±0.8*	1.8±0.5

Notes: Data are expressed mean ± standard deviation (SD). *Significant (P < 0.05) when compared against Junior group (One-way ANOVA). **Significant (P < 0.01) when compared against Junior group (One-way ANOVA). The numbers in parentheses indicate the number of animals examined.

Changes in Serum Metabolites

As shown in Table 2, serum GLU concentrations in Mature, Senior, and Geriatric-obese groups were significantly higher than those in Junior group (mean ± SD, 139.1±48.4137.7 ± 29.5150.3 ± 58.2 mg 100 mL^{-1} vs 103.9 ± 20.3 mg 100 mL^{-1}, P value 0.028, P value 0.001, P value 0.031) respectively.

Serum TG concentrations in Senior group were significantly increased compared with those in Junior group. (137.5±146.3 mg 100 mL^{-1} vs 44.2±32.1 mg 100 mL^{-1}, P value 0.029). Serum BUN concentrations in Geriatric-obese and Geriatric-thin group were significantly increased compared to those in Junior group (57.7± 30.1 mg 100mL^{-1}, 31.7±2.1 mg 100 mL^{-1}vs 26.1± 4.2 mg 100 mL^{-1}, P value 0.001, P value 0.048) respectively.

Changes in Inflammatory Biomarker

As shown in Table 2, SAA concentrations in Geriatric-thin group were significantly increased compared to those in Junior group (215.1 ng mL^{-1} vs 28.2 ±54.3 ng mL^{-1}, P value 0.010). As shown in Table 4, 3 of 8 cats with clinical symptoms showed high levels of SAA concentrations with > upper detection limit (15 ng/mL^{-1}). Five of 8 cats with clinical symptoms showed 218.4 ng mL^{-1}, 486.4 ng mL^{-1}, 601.4 ng mL^{-1}, 206.0 ng mL^{-1}, 265.8 ng mL^{-1}, respectively using 100-fold diluted sera.

Changes in Energy Metabolism Marker

As shown in Table 2, malate dehydrogenase/lactate dehydrogenase (M/L) ratio, as an energy metabolic indicator, decreased with aging although statistical significances were not shown.

Changes in Serum Adiponectin

As shown in Table 2, significant differences in serum ADN concentrations were not shown among Junior (5.9 ±4.1 μg mL^{-1}), Prime (5.2 ±3.8 μg mL^{-1}), Mature (4.7 ±2.7 μg mL^{-1}), Senior (3.8±4.2 μg mL^{-1}) Geriatric-obese (7.3±1.4 μg mL^{-1}) or Geriatric-thin (5.0±1.1 μg mL^{-1}) groups.

The Profile of Biomarkers of 8 Cats with Clinical Symptoms

As shown in Tables 3 and 4, 8 cats showed clinical symptoms with high serum SAA levels. Seven of 8 cats were affected with periodontal disease.

Correlation Coefficients and P values Between Age and Examined Parameters

As shown in Table 5, correlation coefficients and P values between age and examined parameter were calculated by multivariate regression analysis. Positive weak correlations between age and GLU (coefficient 0.351, P value 0.003), SAA (coefficient 0.320, P value 0.013), BUN (coefficient 0.306, P value 0.010) were shown while a negative weak correlation between age and ALB (coefficient −0.306, P value 0.010), ALP (coefficient −0.237, P value 0.049) was shown.

Discussion

In this study, we investigated values of metabolites, enzymes and hormones in serum of 70 domestic cats with various ages. Body weight and BCS of cats increased with aging. In Japan, body condition scores (BCS) of cats are usually examined with a 5-point system. However, this system is vague. In this study, we employed a 9-point system to evaluate in detail. We divided the geriatric group into Geriatric-obese and Geriatric-thin groups since we found two types in the geriatric group. Generally, domestic cats seemed to increase body weight and BCS with aging. In this study, we investigated values of metabolites, enzymes and hormones in serum of 70 healthy cats

Table 3 The Profile of Biomarkers of 8 Cats with Clinical Symptoms

No.	Group	Age (Years)	BW (kg)	BCS	TP	ALB	AST	ALT	ALP	γ-GTP	BUN	CRE	GLU	TG
1	prime	3.6	3.31	5	7.4	2.8	24	39	69	0.5	31	2.1	83	21
2	prime	5.6	5.58	7	6.5	3	30	58	52	0.1	20	1.4	95	16
3	Mature	9.3	5.06	7	7.2	3.4	15	30	66	0.6	21	1.4	73	23
4	Mature	10.7	5.00	8	8	3	21	36	101	0.1	20	1	154	35
5	Senior	12.3	5.75	6	8.4	3.4	18	47	53	0.7	24	1.3	173	44
6	Senior	13.2	2.80	4	8.3	2.8	27	28	68	0.1	19	1.1	107	9
7	Geriatric-obese	15.8	3.38	5	7.1	2.7	32	29	59	0.3	100	3.5	96	25
8	Geriatric-thin	16.2	2.72	3	7.2	3.2	17	30	54	0.2	34	1.4	152	17

Table 4 The Profile of Biomarkers of 8 Cats with Clinical Symptoms

No.	Group	SAA	ADN	LDH	MDH	M/L	Clinical Symptoms
1	prime	over	7.2	43.3	107.6	2.483	Periodontal disease (mild calculus, gingivitis)
2	prime	over	5.3	38.2	8.1	0.211	Periodontal disease (mild calculus), kidney internal structure irregularity
3	Mature	218.4	4.0	43.3	12.6	0.290	Periodontal disease / Recurrent cystitis
4	Mature	486.4	3.9	61.2	6.3	0.102	Hyperglycemia (stress?) L1 vertebral deformity, mild periodontal disease
5	Senior	601.4	2.2	66.3	1.8	0.027	Hip dysplasia, periodontal disease, pancreatitis in the past, hyperglycemia (stress?)
6	Senior	206.0	2.0	132.6	13.5	0.101	Early renal function decline
7	Geriatric-obese	265.8	8.4	45.9	14.4	0.313	Moderately impaired renal function / periodontal disease / traumatic hair loss
8	Geriatric-thin	over	5.0	17.8	9.0	0.502	Bacterial cystitis (bacterial bladder infection), pancreatic tumor,6 lumbar vertebrae (congenital), binocular sclerosis, periodontal disease

Table 5 Correlation Coefficients and P values Between the Age and Examined Parameters in This Study

Correlation	Coefficient	P value
BCS (70)	0.035	0.771
GLU (70)	0.351	0.003**
TG (66)	0.192	0.122
SAA (60)	0.320	0.013*
ADN (64)	-0.131	0.302
TP (70)	0.048	0.693
ALB (70)	-0.306	0.010**
LDH (66)	-0.297	0.016*
MDH (64)	-0.204	0.105
M/L ratio (64)	-0.142	0.263
AST (70)	-0.115	0.341
ALT (70)	-0.193	0.109
ALP (70)	-0.237	0.049*
γGTP (70)	0.128	0.289
CRE (70)	0.156	0.198
BUN (70)	0.306	0.010**

Notes: Correlation coefficients were calculated by multivariate regression analysis. *Significance level was set at $P < 0.05$. **Significance level was set at $P < 0.01$. The numbers in parentheses indicate the number of animals examined.

of various ages. Three of 70 (4.3%) cats investigated were thin at geriatric stage. Almost all cats seemed to increase body weight and BCS with aging. Serum GLU and TG concentrations increased with aging. Nine breeds of cats were recruited in this study. It is difficult to clarify breed difference in aging since there are many influential factors in domestic cats.

In cats, GLU uptake to the liver is considerably lower than dogs since glucokinase activity is lacking in the livers of cats[6] and cats are more prone to suffer from insulin resistance and type 2 diabetes mellitus due to a decrease of the insulin signaling gene (IRS-1, IRS-2 and PI3-K) expression.[8] Cats may tend to be obese compared with dogs.

MDH is a key enzyme for the malate-aspartate shuttle, an NADH shuttle which produces ATPs from glucose metabolism. LDH is an enzyme which catalyzes the conversion of lactate to pyruvate consuming cytosolic NADH. M/L ratio is regarded as a good indicator for evaluating energy metabolism in animals.[17,18] In this study, M/L ratio in Junior group was higher than in the Geriatric group although there was no statistical significance. In healthy cats, energy metabolism (ATP production via glycolysis) seems to attenuate gradually with aging. It now seems evident that the aging process is accompanied by mitochondrial dysfunction in humans and experimental animals.[19]

SAA, an inflammatory marker, gradually increased with aging in healthy cats. SAA, a protein of ~12 kDa, is an acute phase reactant that can be detected in blood when inflammation occurs. In humans, serum SAA concentrations increase up to 1000-fold within 24–48 h after inflammatory stimuli.[20] Feline SAA concentrations are also recognized as a useful inflammatory marker. When inflammation and/or tissue damage occurs, feline SAA concentrations also increase up to 1000-fold.[21] We reported that SAA concentrations significantly increase in cats with obesity.[22] In this study, we observed an increase in high SAA concentrations in geriatric cats. It suggests that some slight inflammation occurs in the body with aging.

We have previously reported serum ADN concentrations tended to decrease in obese cats with visceral fat accumulation.[23,24] However, serum ADN concentrations in geriatric cats in this study are not different from those in other younger cats since their BCS is not significantly different. No adiponectin variation would be expected for healthy geriatric cats.

Serum ALB concentrations in geriatric-obese cats were lower than those in other younger cats. We suggest that

decrease of ALB and M/L ratio may indicate attenuation of liver functions related to nutrition/energy metabolism with aging.

From the above results, serum GLU, TG, SAA, ALB concentrations and M/L ratio seem to be useful markers for detecting small changes related to energy metabolism in aged cats. Chandler reported that the peak age for obesity in cats is between 10 and 12 years old.[25] Therefore, we have to pay much attention to feline health condition at pre-senior stages.

The limitations of this study are as follows. 1) Kitten group (< 6 months) cats according to the AAFP-AAHA Feline Life Stage Guidelines are not recruited in this study. 2) Gender and breed differences on aging are not investigated due to the small number of animals examined. 3) Influences of nutritional factors are not considered since pet foods given from pet owners are varied. 4) Energy metabolic markers, such as 5′adenosine monophosphate-activated protein kinase (AMPK), were not measured in this study.

In this study, we clarified that a part of small changes related to energy metabolism including increases in body weight and BCS result in the occurrence of obesity in healthy cats with aging. These changes seem to be owing to declines in liver and kidney function. Some diagnostic markers such as GLU, TG, SAA, ALB, BUN concentrations and M/L ratio can reflect small reactions related to energy metabolism in healthy cats. These phenomena may suggest that energy metabolism in liver and kidney may be attenuated with slight inflammation in aged cats.

Conclusion

Healthy cats tend to increase their body weight and BCS with aging. These changes seem to be owing to attenuation related to energy metabolism in their liver and kidneys. In healthy cats, serum GLU, TG BUN, and SAA concentrations increased and serum ALB concentrations and M/L ratio decreased. These diagnostic markers may be useful to detect small changes related to energy metabolism with aging which can cause obesity with light inflammation in healthy cats.

Abbreviation

ADN, adiponectin; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMPK, 5′-adenosine monophosphate-activated protein kinase; AST, aspartate aminotransferase; BCS, body condition score; BMI, body mass index, BUN, blood urea nitrogen; BW, body weight; CRE, creatinine; GLU, glucose; γ-GTP, γ-glutamyl transpeptidase; IRS-1, insulin receptor substrate-1; IRS-2, insulin receptor substrate; LDH, lactate dehydrogenase; MDH, malate dehydrogenase; M/L, malate dehydrogenase/lactate dehydrogenase; NADH, nicotinamide adenine dinucleotide; PIP3-K, phosphatidylinositol3-kinase; SAA, serum amyloid A; SD, standard deviation; TG, triglyceride; TP, total protein.

Disclosure

The authors report no conflicts of interest and declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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