



Concentrations of leptin, adiponectin, and resistin in the serum of obese cats during weight loss

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ABSTRACT. We monitored changes in serum leptin, adiponectin, and resistin concentrations in obese cats during weight loss. Six naturally developed obese cats were fed low-fat, high-fiber dry food during a 9-week experimental period. Serum leptin, adiponectin, and resistin concentrations were measured at week 0, 4, 8, and 9. Body weight became significantly lower week 4 onward than that at week 0 ($P < 0.05$ or 0.01). At week 9, serum leptin concentrations were significantly lower than those at week 0 ($P < 0.05$). Contrarily, serum adiponectin and resistin concentrations did not significantly differ within the 9 weeks. While serum leptin levels were strongly positively correlated with body weight ($r = 0.923$, $P < 0.001$), serum adiponectin levels were moderately negatively correlated with it ($r = -0.529$, $P < 0.01$), with serum resistin having a no correlation with body weight. Serum leptin levels might be more closely related with pathogenesis of adiposity than serum adiponectin or resistin in cats.

KEY WORDS: adiponectin, cat, leptin, resistin, weight loss

J. Vet. Med. Sci.

81(9): 1294–1300, 2019

doi: 10.1292/jvms.19-0091

Received: 13 February 2019

Accepted: 21 July 2019

Advanced Epub: 1 August 2019

Obesity in domestic cats has been a prevalent veterinary medical problem in recent years [15] and is linked to numerous health problems in cats, including an increased risk for metabolic disorders such as diabetes, hyperlipidemia, and hypertension. Efforts attributing to weight loss for the treatment of obesity can lead to a reduced risk of diabetes [31].

Some of the most important factors contributing to the pathogenesis of obesity include adipokines, i.e., cytokines produced by adipose tissue. Leptin, adiponectin, and resistin are cited as representative adipokines [2, 28]. Leptin is a classic adipokine suppressing appetite and increasing energy expenditure via binding of its receptor in the brain [28]. Adiponectin plays an important role in increasing insulin sensitivity by stimulating the phosphorylation of 5' AMP-activated protein kinase that activates glucose uptake into cells by promoting translocation of glucose transporter type 4 [28]. Resistin is believed to be involved with obesity-related insulin resistance and metabolic derangements [10, 28]. Obesity in humans can alter the production or regulation of these adipokines, leading to increased risks of metabolic syndromes, type 2 diabetes, atherosclerosis, heart disease, and cancer [25, 36]. Thus, to make an adequate risk assessment for the development of complications related to obesity, analysis of adipokines and their relationships is important.

These adipokines have also been investigated in cats. Several studies reported that blood leptin levels reflect body fat mass [3, 4, 32], and conversely, weight loss is associated with a decrease in leptin levels [17]. Some studies reported that serum adiponectin concentrations decrease with obesity and increase with weight loss [16, 17, 37], while others reported no differences in serum adiponectin among lean and obese cats [6, 38]. Most studies only reported comparisons between individuals, or within single subjects before and after weight loss or gain. In particular, studies comparing individuals could be influenced by factors other than the degree of obesity, and it could be problematic to draw conclusions concerning the relationship between the adipokines and obesity. In addition, two-point data, i.e., before and after weight alteration, might be less reliable than multipoint data within the same individual. These represent some of the problems of previous studies on feline leptin and adiponectin. Furthermore, there are no studies reporting blood resistin concentration in cats. Revealing changes in serum adipokine concentrations during weight fluctuation in the same individual would contribute to understanding the pathophysiology of feline obesity. In the present study, we monitored changes in serum leptin, adiponectin, and resistin concentrations for 9 weeks in naturally developed obese cats during weight loss.

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MATERIALS AND METHODS

Animals

Animal experiments were carried out at the KITAYAMA LABES facilities. All experiments were reviewed and approved by the institutional animal welfare committee (Approval No. NBC-54-025). Six obese cats (four intact and two spayed females, 8.5 ± 0.8 years old) were maintained at the KITAYAMA LABES. Mean body weight was 4.43 ± 0.56 kg and median body condition score was 5 (range, 4–5) on a 5-point scale. Cats were primarily used for palatability testing, and their obesity was naturally developed by the feeding of dry foods with no caloric supplementation prior to inclusion in the present study. Cats were determined to be healthy based on physical examination, appetite, CBC, and biochemistry before the experiment. The cats were kept in individual cages in an animal house with a 12:12 hr light:dark cycle, and temperature range of 20–25°C.

Study design

During the 9-week experimental period, cats were fed a low-fat, high-fiber dry food (JP Style Dietics Slim Support, Nisshin Pet Food, Tokyo, Japan), formulated according to nutritional standards for adult cats by the Association of American Feed Control Officials 2016. To achieve weight loss, the cats received food once daily at 80% of the resting energy requirement, calculated based on the estimated ideal body weight [8]. Cats were given unlimited access to water throughout the experiment period. Food consumption was weighed daily, body weight was measured weekly, and fasting blood samples were collected at baseline and at 4, 8, and 9 weeks after the experiment initiation. The EDTA blood and serum samples were stored at 4°C and used for complete blood count and biochemical analyzes, respectively. Aliquots of serum samples were stored at –80°C until conducting measurements for leptin, adiponectin, resistin, and insulin concentrations.

Assays

Complete blood count and biochemical analyzes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, urea nitrogen, creatinine, total protein, albumin, total cholesterol, triglyceride, glucose, calcium, inorganic phosphate, sodium, potassium, and chlorine) were carried out at a commercial laboratory (LSI Medience Corp., Tokyo, Japan) using an automated hematology analyzer (XT-2000iV, Sysmex, Hyogo, Japan) and automated biochemical analyzer (JCA-BM-6050, JEOL, Tokyo, Japan). Serum leptin concentrations were determined by RIA kit (Multi-specied leptin RIA kit, Millipore, St. Charles, MO, U.S.A.). Serum adiponectin (Murine/rat adiponectin ELISA kit, Otsuka Pharmaceutical, Tokyo, Japan), resistin (RayBio Feline Resistin ELISA kit, RayBiotech, Norcross, GA, U.S.A.), and insulin (Feline insulin ELISA, Mercodia, Uppsala, Sweden) concentrations were measured by ELISA carried out in duplicate on a single plate. For the resistin assay, the intra-assay coefficient of variation was 3.6–6.1%. Measurement range of feline resistin was 0.012–3.0 ng/ml, and the linearity of resistin ELISA was confirmed by 2-fold serial dilution of two plasma samples derived from clinically healthy cats. Experiment with serum samples spiked with resistin standard (0.01, 0.025, 0.64, and 0.16 ng/ml) resulted in a recovery of 98.3% (range 85.0–110.4%; $n=2$). Assays for serum leptin, adiponectin, and insulin have been previously validated in cats [11, 17, 18, 23, 34].

Statistical analysis

Differences in parameters from before and during the experiment were analyzed by one-way repeated measures ANOVA with Bonferroni-adjusted pairwise comparisons. A difference in BCS between baseline and throughout the experiment time course was analyzed by a Friedman test with Bonferroni-adjusted Wilcoxon signed rank test. Correlations between body weight or serum insulin and serum leptin, adiponectin, and resistin concentrations were analyzed by Pearson's correlation coefficient. *P*-values <0.05 were considered statistically significant. All analyzes were performed using R software (The R Foundation for Statistical Computing, version 3.0.2) with a graphical user interface (EZR, Saitama Medical Center, Jichi Medical University, Japan) [19].

RESULTS

After the initiation of the experiment, body weight began to decrease until week 9 (Table 1). The weight reduction rate was between 0.5 and 1.8% per week. At week 4, body weight was lower than that at week 0 ($P<0.05$ or 0.01). At week 9, cats had lost

Table 1. Changes in parameters during weight loss in 6 cats

Parameters	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
Body weight (kg)	4.43 ± 0.56	4.35 ± 0.55	4.33 ± 0.57	4.27 ± 0.57	4.24 ± 0.56 ^{a)}	4.21 ± 0.57 ^{b)}	4.18 ± 0.57 ^{b)}	4.15 ± 0.57 ^{b)}	4.10 ± 0.58 ^{b)}	4.07 ± 0.59 ^{b)}
Weight reduction rate from preceding week (%/week)		1.76	0.50	1.29	0.86	0.60	0.79	0.68	1.16	0.69
Body condition score (5–points scale)	5 (4–5)	5 (4–5)	5 (4–5)	5 (4–5)	4.5 (4–5)	4.5 (3–5)	4.5 (3–5)	4.5 (3–5)	4.5 (3–5)	4.5 (3–5)
Daily food consumption (g)	42 ± 7.0	44 ± 4.6	42 ± 7.2	42 ± 8.0	43 ± 6.8	43 ± 6.7	43 ± 6.2	43 ± 6.7	42 ± 8.4	40 ± 9.5

Body weight and daily food consumption are indicated as mean ± SD. Body condition score is indicated as median (range). a) $P<0.05$ and b) $P<0.01$ when compared with the value at week 0.

8.1 ± 2.6% of their body weight compared to baseline. BCS tended to decrease during the experiment, however, the change was not statistically significant. Daily food consumption was kept stable during the experimental period. CBC, serum biological parameters, and serum insulin concentrations showed no alteration during the examination (Table 2).

Serum leptin concentrations gradually decreased during the experimental period, and by week 9 became lower than those from before the experiment ($P < 0.05$; Fig. 1A). On the other hand, serum adiponectin and resistin concentrations did not show significant changes during the 9 weeks (Fig. 1B and 1C).

Serum leptin concentrations showed a strong positive correlation with body weight ($r = 0.923$; 95% confidence interval, 0.827–0.966; $P < 0.001$; Fig. 2A). Conversely, serum adiponectin showed a moderate negative correlation with body weight ($r = -0.529$; 95% confidence interval, -0.768 to -0.159 ; $P < 0.01$; Fig. 2B). Serum resistin concentration did not display a correlation with body weight (Fig. 2C). Serum insulin showed a negative correlation with serum resistin ($r = -0.501$; 95% confidence interval, -0.752 – -0.122 ; $P < 0.05$; Fig. 3C), but not with serum leptin and adiponectin (Fig. 3A and 3B).

DISCUSSION

In the present study, naturally developed obese cats lost approximately 8% of their body weight by dietary management using a low-fat, high-fiber diet. A human report [41] demonstrated that weight loss of >2% of body weight per week is harmful to health because of more loss of lean tissue (skeletal muscle). In a previous report on obese cats [9], weight loss of <1.5% of body weight per week was not accompanied with depletion of non-adipose tissues and was not harmful to metabolism. In the present study, considering that weight loss was approximately 0.8% per week, the cats might have ideal healthy weight loss. This interpretation was supported by stable food consumption and an absence of variation in serum creatinine, reflecting muscle volume during weight loss. Therefore, we were able to obtain data on serum adipokine changes during healthy weight loss in obese cats.

Serum leptin concentrations gradually decreased along with weight loss, and by the end of the experiment, they became significantly lower than those prior to weight loss. Decreased serum leptin concentrations after weight reduction were consistent with previous studies [17, 39]. In addition, serum leptin concentrations were positively and strongly correlated with body weight. Since weight loss in obese cats represents a change in fat mass, our results were consistent with previous studies, demonstrating that blood leptin concentrations are directly proportional to the percent of body fat in cats [4, 17, 32]. Obesity is characterized by a syndrome of at least partial leptin resistance and hyperleptinemia, contributing to the development of a variety of comorbidities associated with obesity, including cardiac, renal, and vascular dysfunction [28]. In obese cats, periodic measurements of serum leptin during weight loss might be useful as a monitoring tool for the improvement of the pathogenesis of obesity.

In the present study, serum adiponectin concentrations did not significantly change during the 9-week experimental period. In contrast, previous reports have demonstrated significant increases in blood adiponectin with weight loss in obese cats [17, 37]. In addition, it has been shown that cats displayed decreased plasma adiponectin after weight gain [16]. These discrepancies

Table 2. Changes in hematological and biochemical parameters during weight loss in six cats

Parameters	Week 0	Week 4	Week 8	Week 9	Reference range
White blood cells ($\times 10^3/\mu\text{l}$)	9.5 ± 2.2	9.6 ± 1.6	11.2 ± 2.3	11.3 ± 1.7	5.5–19.5
Red blood cells ($\times 10^6/\mu\text{l}$)	9.6 ± 1.2	9.2 ± 0.7	9.2 ± 0.7	9.1 ± 0.6	5.0–10.0
Hemoglobin (g/dl)	14.7 ± 2.1	13.9 ± 1.1	13.7 ± 1.0	13.4 ± 1.0	8.0–15.0
Hematocrit (%)	44.4 ± 6.7	42.4 ± 3.8	42.1 ± 3.5	42.0 ± 3.4	24–45
Platelet ($\times 10^3/\mu\text{l}$)	29.7 ± 8.7	36.8 ± 7.3	35.6 ± 11.6	47.2 ± 8.6	30–80
Alanine aminotransferase (U/l)	60.2 ± 17.3	58.2 ± 13.9	59.0 ± 14.3	62.7 ± 12.7	20–122
Aspartate aminotransferase (U/l)	22.2 ± 9.0	19.5 ± 4.6	18.8 ± 9.0	18.8 ± 5.2	6–48
Alkaline phosphatase (U/l)	86.0 ± 19.6	65.5 ± 9.1	67.3 ± 8.4	70.3 ± 10.0	30–228
Total bilirubin (mg/dl)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0–0.1
Urea nitrogen (mg/dl)	21.7 ± 1.2	20.0 ± 2.7	20.0 ± 2.4	19.5 ± 2.0	17–40
Creatinine (mg/dl)	1.22 ± 0.22	1.22 ± 0.21	1.23 ± 0.22	1.22 ± 0.22	0.8–2.2
Glucose (mg/dl)	83.8 ± 14.5	75.2 ± 10.3	81.8 ± 13.2	86.7 ± 24.1	58–132
Total protein (g/dl)	7.1 ± 0.7	7.0 ± 0.6	7.1 ± 0.5	6.9 ± 0.5	6.1–8.4
Albumin (g/dl)	3.5 ± 0.3	3.5 ± 0.3	3.4 ± 0.3	3.3 ± 0.3	2.9–4.3
Total cholesterol (mg/dl)	106.3 ± 17.6	101.8 ± 14.1	105.2 ± 18.4	103.5 ± 17.5	98–264
Triglyceride (mg/dl)	17.0 ± 4.6	15.5 ± 5.0	15.5 ± 3.6	15.5 ± 2.9	14–120
Calcium (mg/dl)	9.4 ± 0.6	9.3 ± 0.5	9.2 ± 0.6	9.3 ± 0.5	9.0–11.2
Inorganic phosphate (mg/dl)	4.4 ± 0.5	4.5 ± 0.5	4.6 ± 0.7	4.8 ± 0.6	2.6–6.2
Magnesium (mg/dl)	2.3 ± 0.1	2.2 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	2.2–2.9
Sodium (mmol/l)	154.8 ± 1.8	154.8 ± 2.5	154.2 ± 3.1	154.8 ± 2.9	148–155
Potassium (mmol/l)	4.5 ± 0.2	4.4 ± 0.3	4.5 ± 0.3	4.6 ± 0.4	3.5–5.2
Chlorine (mmol/l)	119.3 ± 2.7	119.7 ± 2.3	120.5 ± 2.3	121.0 ± 2.3	115–124
Insulin (ng/l)	112.1 ± 29.2	83.8 ± 16.9	97.0 ± 18.6	89.1 ± 12.6	

Data are presented as mean ± SD.

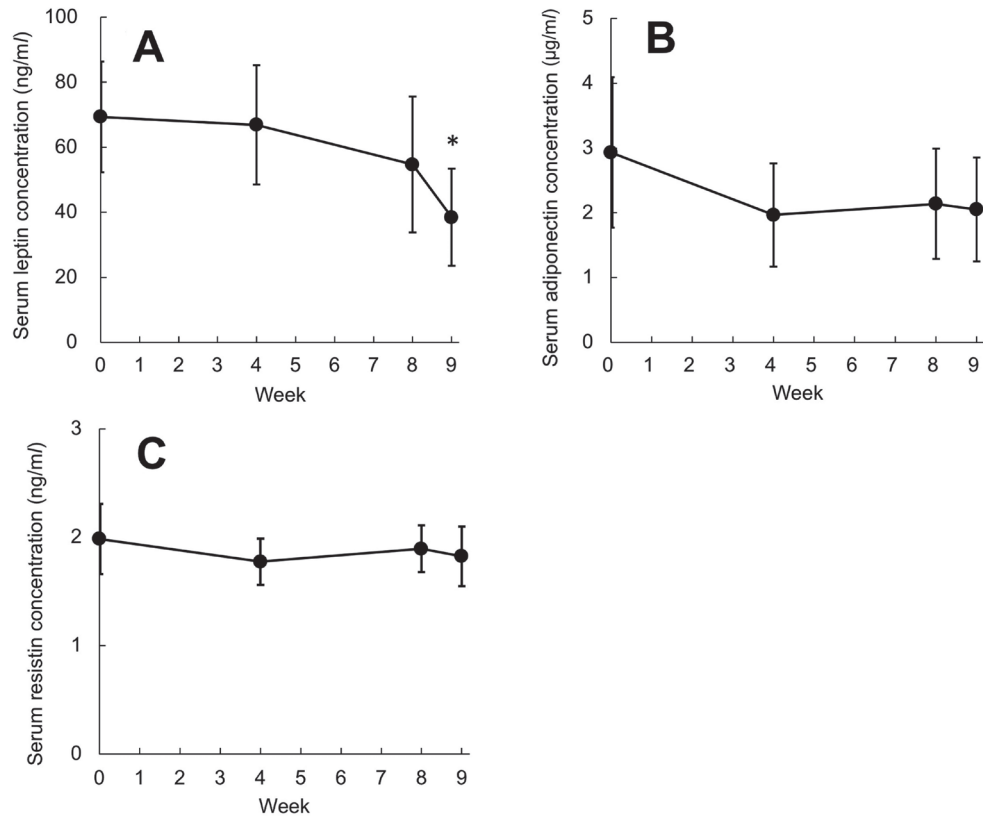


Fig. 1. Serum leptin (A), adiponectin (B), and resistin (C) concentrations during weight loss in six cats. Data are indicated as mean \pm SEM. *Significantly different from the value at week 0 ($P < 0.05$).

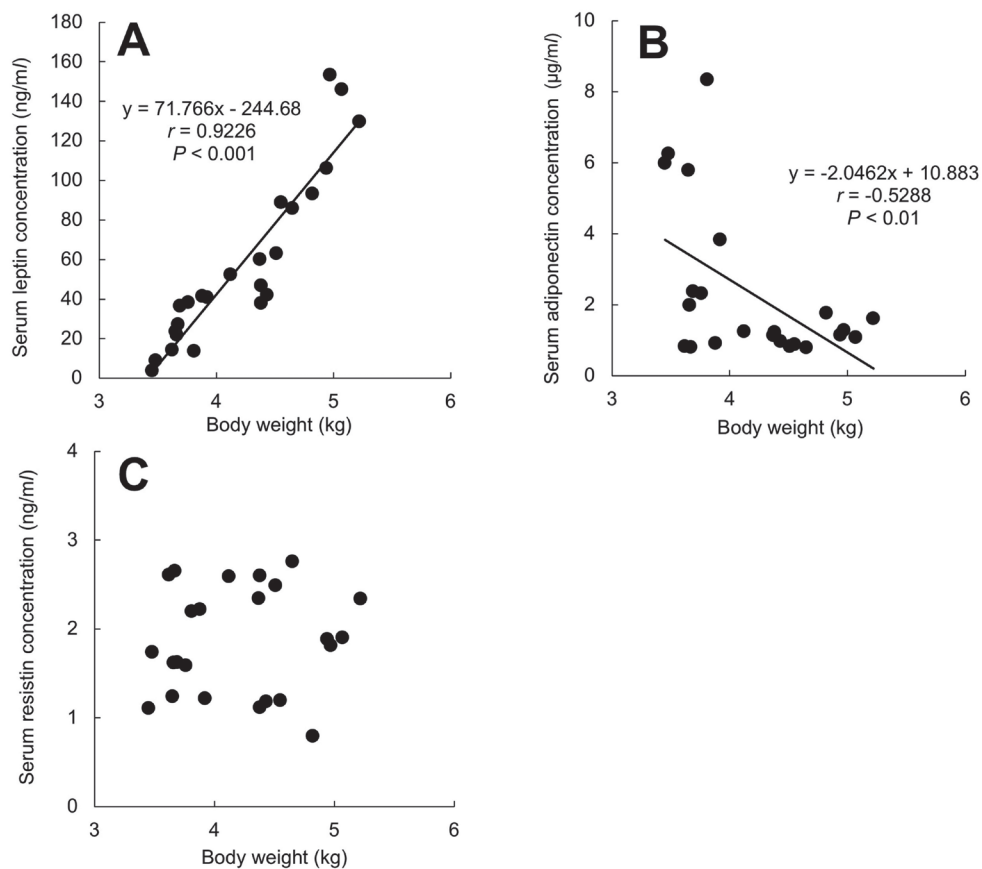


Fig. 2. Relationships between body weight and serum concentrations of leptin (A), adiponectin (B), and resistin (C).

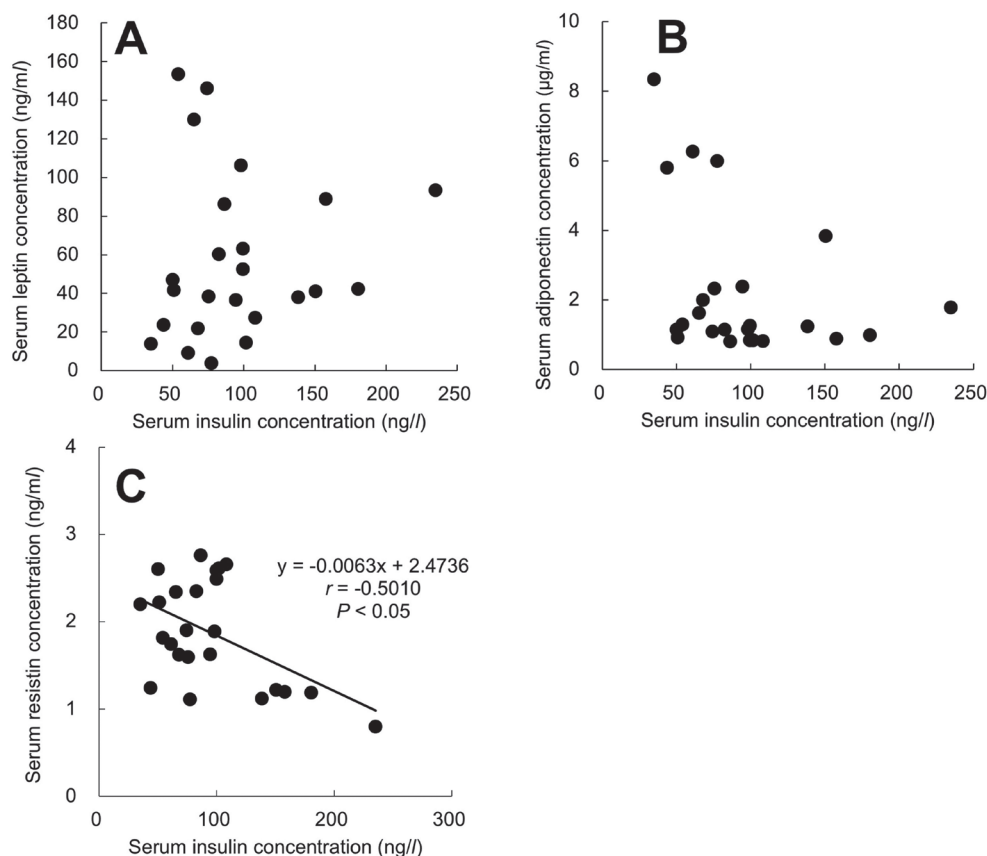


Fig. 3. Relationships between serum concentration of insulin and leptin (A), adiponectin (B), and resistin (C).

concerning serum adiponectin concentrations within the current and previous studies could be attributed to the magnitude of changes in body weight during experiments between differing studies. In our 9-week study, weight loss during the experimental period equaled approximately 8% of starting weight, whereas these values totaled greater than 20% within previous studies of durations greater than 8 months [17, 37]. Increased weight loss or longer experimental time periods could have caused these varying results in serum adiponectin concentrations. Another contributing factor could be molecular-specific changes in serum adiponectin concentration; adiponectin in circulation composes a multimer formation of low-, middle-, and high-molecular-weights [40]. Recent studies in humans show that the high-molecular-weight form of adiponectin is more closely associated with insulin resistance and diabetes-linked obesity than total adiponectin or low-molecular-weight forms [13, 26]. One feline study reported that total blood adiponectin remained unaltered despite weight loss of over 20%, whereas blood high-molecular-weight form of adiponectin was correlated with fat mass [42]. Since the present study evaluated only total adiponectin in serum, the measurement of serum molecular weight-specific adiponectin concentrations during weight loss could provide further information concerning the relationship between serum adiponectin and fat mass. Considering that adiponectin has a role in enhancing insulin sensitivity [28], there is a possibility that adiponectin is related with fasting insulin concentration. However, in the present study, there was no correlation between adiponectin and insulin. The analysis in diabetic cats on reduced insulin sensitivity and molecular weight-specific adiponectin might elucidate the relationship between adiponectin and insulin. In any case, our results showed that these adiponectin concentrations are less sensitive to body weight changes than serum leptin concentrations within cats. Interestingly, the serum adiponectin concentrations were negatively correlated with body weight, despite the lack of increase of adiponectin concentrations that accompanied weight loss. This negative correlation of adiponectin concentration with body weight is consistent with previous studies [17, 38], however, a correlation independent of a change of weight has not been reported. This could suggest that serum adiponectin is influenced by factors associated with body weight other than the degree of obesity, which resulted in the individual difference. This hypothesis is supported by previous studies in humans, in which higher serum adiponectin levels were associated with low muscle mass [5, 22]. Unfortunately, it was beyond the scope of the present study to elucidate the mechanisms potentially affecting serum adiponectin concentrations in cats.

To the best of our knowledge, this study is the first to report serum resistin concentrations in cats. Although circulating levels of resistin increase along with progression of obesity in rodent models [20], in cats, it did not significantly change during weight loss within the 9-week experimental period of this study, and its concentration did not correlate with body weight. In rodents, resistin is secreted by adipocytes and is confirmed to have restricted expression in adipocytes [33]. However, in humans, resistin is predominantly produced by non-adipocytes such as monocytes/macrophages [27], and increased blood level in resistin is caused by

secretion from macrophage-invaded adipocytes [12, 24]. Recent evidence in humans suggests that the serum resistin concentration does not reflect the degree of obesity [1, 7, 14, 21]. According to our unpublished data, feline resistin mRNA is expressed not only in adipose tissue, but also within the lung and spleen. Our previous report described that obese cats had higher resistin mRNA expression in adipose tissue than normal cats [35]. This may reflect obesity-induced macrophage infiltration into adipose tissue; however, increased resistin expression in adipose tissue does not cause hyperresistinemia in cats. Although tissue distribution is different among species, resistin is thought to cause insulin resistance via endocrine signaling, or autocrines/paracrines in both rodents and humans. As the serum resistin concentration did not alter during weight loss in cats, a local contribution of resistin for obesity-induced pathology could not be excluded. In the present study, a negative correlation between serum resistin and insulin was noted in cats. It is inconsistent with previous reports suggesting that resistin causes insulin resistance [10, 29]. However, it is also reported that resistin suppressed the secretion of insulin in rats [30]. Suppression of insulin secretion by resistin might explain the negative correlation between insulin and resistin in healthy cats. Investigating the relationship between circulating resistin and insulin concentrations in diabetic cats during weight loss might provide further information.

The present study demonstrated serial changes in serum leptin, adiponectin, and resistin in individual obese cats during a 9-week weight loss period. In obese cats, weight reduction induced a clear decrease in serum leptin, but did not alter adiponectin or resistin levels. Therefore, leptin might be more closely related with the pathogenesis of adiposity than serum adiponectin or resistin in cats.

CONFLICT OF INTEREST. This study was funded by Nisshin Pet Food.

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