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Physiological Changes Following Acute Weight Gain and Loss in Cats

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Research Article

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ABSTRACT

Introduction: Prevalence of obesity is increasing in cats as in humans. As obesity is a risk factor for severe metabolic disorders such as diabetes and hyperlipidemia, early detection and prevention of overweightness and obesity are valuable. Development of new diagnostic markers is useful for early detection for obesity in animals.

Objects: Body Condition Score (BCS) is commonly used to evaluate weight status in veterinary medicine, but it can be subjective and may not accurately reflect the true metabolic status of an animal. To evaluate the usefulness of metabolome, hormone, and enzyme markers as the indicators for early obesity, changes in various parameters were measured during the experimentally induced acute weight gain and loss in cats and their correlations to the changes in BCS and body weight (BW) were closely analyzed.

Methods: 6 healthy mixed-breed cats were used and fed high-fat diet and restricted-calorie diet to induce acute weight gain and weight loss respectively. Changes in BW, BCS and plasma levels of metabolome, hormones, enzyme parameters, and adipokines were measured during the weight gain and loss periods.

Results: Significant elevations associated with weight gain were seen in Triglyceride (TG), Alanine Aminotransferase (ALT), adiponectin, Malondialdehyde (MDA) in cats. Highest BCS was associated with the highest values of Triglyceride (TG), Aspartate Aminotransferase (AST), adiponectin, and with the lowest values of TNFα.

Conclusion: The results suggest that acute weight gain and high BCS in cats may not necessarily be pathological as long as adiponectin and anti-oxidant protection of the body are in effect. At an early phase of acute weight gain, body's protection against pro-inflammatory and oxidative effects of adiposity remain functional, keeping overweight individuals metabolically healthy even at high BCS.

INTRODUCTION

With the increasing prevalence of obesity in companion animals [1], public awareness for obesity as a risk factor for metabolic diseases, orthopedic disease, neoplasia, and shorter life span has risen more than ever [2,3]. Additionally, there is a recent developing concept that obesity is accompanied by chronic low-grade systemic inflammation, caused by increased insulin resistance and production of inflammatory mediators, which in turn, contributes to the onset of obesity-related diseases [4,5]. Early detection and prevention of overweight and obesity is of great public concern globally. However commonly accepted evaluation method of weight status in veterinary medicine is a 5-point or 9-point Body Condition Score (BCS) [6,7], which is a semi-quantitative assessment method employing visual observation and palpation of subcutaneous fat by an observer. Such subjective weight status assessment may be affected by inter-observer variation and may not faithfully reflect the true metabolic health status of an

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individual. Therefore, it may confound the point where early medical and/or environmental intervention is warranted to prevent obesity-related diseases.

The reliability of BCS in detecting abnormality in metabolic health needs to be re-evaluated and the point when weight gain becomes pathological should be identified. Previously, many researchers have introduced various quantitative parameters such as lipid concentrations [8,9], lipoprotein profiles [10,11], oxidized low-density lipoprotein [12], and their reference values to evaluate the quality of weight gain. Furthermore, our team has evaluated the usefulness of adiponectin measurement, Visceral Adipose Tissue (VAT) and adipocyte size assessment as the tools to classify obesity in cats as "pathological" or "simple" [13]. In this study, 6 cats were experimentally over fed for 4 weeks, then provided restricted amount of weight control diet for 4 weeks. The aim of this study are to follow the changes in biochemical markers such as metabolome markers, especially adiponectin, pro-inflammatory cytokine, oxidative stress markers, and hormones, and to explore the relationships between these and BCS in the animals. This was the preliminary effort to evaluate the biochemistry during experimentally induced acute weight changes in cats in order to confirm the presence/absence of pathological effects of weight gain in a short-term acute weight changes

MATERIALS AND METHODS

Animals

6 healthy mixed-breed laboratory cats (Neutered males, 41.0 ± 1.0 months, 4.26 ± 0.27 kg, BCS=3.0 ± 0.3) were utilized in this study. For the first 4 weeks, all of the cats were provided high-fat dry diet (Nippon Pet Food Co., Ltd., Tokyo, Japan) at 2.0 × the amount of Daily Energy Requirement (DER=1.4 × 70 × bodyweight 0.75) per day, in two separate feedings (8:00 AM, 4:00 PM) in order to induce experimental weight gain. DER was calculated by resting energy requirement (RER=70 × Bodyweight 0.75) multiplied by a factor to account for normal activity for intact adult cats. After the weight-gain period, the same group was provided low-fat dry diet (Nippon Pet Food Co., Ltd., Tokyo, Japan) at the amount equivalent to DER for 2 weeks in order to avoid sudden drop in caloric intake, then provided 0.8 (factor for weight loss) × the amount of resting energy requirement (0.8 × 70 × bodyweight 0.75) for 2 weeks to induce weight reduction. Water was given ad libitum throughout the study period. The product information of both high-fat dry diet and low-fat diet is as shown in **Table 1**. The daily food consumption of each cat was calculated by subtracting the amount of leftover food from the amount of supplied food. All the cats were kept individually in cages measured 540 mm × 450 mm × 720 mm and provided the same condition at Narita Animal Science Laboratory Co., Ltd. (Narita, Japan), with the environment maintained at 24.0 ± 2.0˚C and 55.0 ± 10.0% relative humidity, and on a 12:12 h, light: dark cycle (light on 8:00 AM to 8:00 PM). Ethical approval for this study was from Narita Animal Science Laboratory Co., Ltd. Research Animal Ethical Committee (15-F043).

Table 1. Macronutrient comparison of the diets.

Guaranteed amount (%)	High-fat diet[#]	Low-fat diet[##]
Moisture	6.6	7.8
Protein	29.1	39.3
Fat	25.6	10.2
Crude fiber	2.1	8
Ash	5.8	6.3
Nitrogen free extract	30.8	28.4
Energy (kcal ME/100 g)*	469.9	362.6

*Calculated by using Atwater factors

[#]High-fat diet consists of the following ingredients: Corn, meat meal, bee oil, corn glutenmeal, wheat flour, tapica pregelatinized starch, vitamin mineral premix, chicken meal, pal oil, fish oil, chicken oil, phosphoric acid, yeast cell wall, DL-methionine, oligosaccharide, collagen powder, choline chloride, vitamin E, vitamin C

[##]Low-fat diet consists of the following ingredients: Meat meal, corn gluten meal, corn, cellulose powder, wheat flour, high DHA seaweed powder, vitamin mineral premix, whey protein concentrate powder, soybean and rapeseed oil, fish powder, L-lysine, aminoesthylsulfonic acid, vitamin E, choline chloride, DL-methionine, vitamin C, L-carnitine, antioxidant, high selenium yeast

Body Weight and Body Condition Score

Bodyweight and BCS were measured at the time of each blood collection. Each subject was evaluated by the same veterinarian on-site, and was classified by a 5-point BCS scale, a system most commonly used in Japan, with: 1) Very thin, 2) Underweight, 3) Ideal, 4) Overweight, and 5) Obese.

Collection and Preparation of Blood Samples

5 ml of blood was collected from the jugular vein of each animal into the heparinized tubes before the experiment (0 week), 2 weeks into the hight fat diet feeding (2 weeks), at the end of weight gain period (4 weeks), 2 weeks into the mild weight reduction period (6 weeks), and at the end of the weight reduction period (8 weeks). Blood collection was performed before the morning

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feeding and the collected blood samples were immediately centrifuged at 2,000 g for 10 min, 4˚C. These samples were stored at -80˚C until use.

Plasma Parameters

Plasma concentrations of Glucose (GLU), TG, Total Cholesterol (TC), Total Protein (TP), Blood Urea Nitrogen (BUN), and Creatinine (CRE), activities of Alkaline Phosphatase (ALP), ALT, AST, lactate dehydrogenase (LDH) were measured using an auto analyzer (JCA-BM2250, JEOL Ltd., Tokyo, Japan) with the manufacture's reagents at Monolis Inc. (Tokyo, Japan). Plasma Non-Esterified Fatty Acid (NEFA) concentration was measured using a commercial kit, NEFA-C test (Wako Pure Chemical Industries, Inc., Tokyo, Japan). Plasma insulin, adiponectin, and Tumor Necrosis Factor Alpha (TNFα) concentrations were measured with commercial enzyme-linked immunosorbent assay (ELISA) kits, Lbis dog insulin kit (SHIBAYAGI Co., Gunma, Japan), mouse/rat adiponectin kit (Otsuka Pharmaceutical Co., Ltd, Tokyo, Japan), and Feline TNF-alpha/TNFSF1A DuoSet (R&D Systems, Inc., Minneapolis, USA), respectively. NWLSSTM Malondialdehyde (MDA) assay (Northwest Life Science Specialties, LLC, Vancouver, Canada) was utilized to measure MDA concentration. Plasma Super Qxide Dismutase (SOD) and Glutathione Peroxidase (GSHPx) activities were measured using commercial kits, NWLSSTM Superoxide Dismutase Activity Assay (Northwest Life Science Specialties, LLC, Vancouver, Canada), and NWLSSTM Glutathione Peroxidase Assay (Northwest Life Science Specialties, LLC, Vancouver, Canada), respectively. All enzymatic activities measured at 24-26°C were expressed as U per volume of plasma (volume activity). The enzyme unit (U) represents 1 μmol of substrate degraded per minute.

Statistical Analysis

All values are expressed as means ± SE and the differences between means compared to the values at 0 week, 4 weeks, and 6 weeks were analyzed by paired t-test. Significance was set up at $p<0.05$.

RESULTS

Changes in mean weight status are shown in **Table 2** as represented by BW (body weight) and BCS. **Table 3** shows BCS changes in each subject (1~6) throughout the study period. An acute increase in mean BCS (BCS=4.3 ± 0.3) was evident during the first 2 weeks (0~2 weeks) of overfeeding, and an acute reduction in weight status was shown in the last 2 weeks (6~8 weeks) of intense calorie restriction. The highest mean weight status was at 4 weeks and the lowest was at 0 week. As shown in **Table 4**, significant elevations associated with weight gain were seen in TG, ALP, ALT, AST, adiponectin, MDA. Highest BCS was associated with the highest values of TG (34.5 ± 4.8 mg/dl), AST (20.5 ± 4.5 IU/l), adiponectin (11.7 ± 1.5 μg/ml), and with the lowest value of TNFα (9.2 ± 5.7 ng/ml). Increase in SOD first appeared at 4 weeks, then reached its highest activity level at 6 weeks (53.8 ± 4.8 IU/ml), then maintained its elevated level through 8 weeks.

Table 2. Changes in body weight (BW) and body condition score (BCS).

	0 week	2 weeks	4 weeks	6 weeks	8 weeks
	Pre	Weight gain stage		Weight loss stage	
BW (kg)	4.2 ± 0.27	5.08 ± 0.30*	5.18 ± 0.40*	5.09 ± 0.32*	4.75 ± 0.3*,#
BCS	3.0 ± 0.3	4.2 ± 0.3*	4.3 ± 0.3*	4.2 ± 0.3*	3.3 ± 0.2#

Values are presented as mean ± SE

*Significantly different ($p<0.05$) from the 0 week values

#Significantly different ($p<0.05$) from the 4 weeks values

Table 3. Changes in BCS in 6 cats.

Cat	0 week	4 weeks	6 weeks	8 weeks
1	3	5	5	4
2	3	5	4	3
3	3	3	4	3
4	4	5	5	4
5	3	4	4	3
6	2	4	3	3

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Table 4. Changes in metabolic marker levels in 6 cats.

Metabolic markers	0 week	2 weeks		4 weeks		6 weeks		8 weeks	
	Pre	Weight gain stage				Weight loss stage			
GLU (mg/dl)	126.2 ± 13.0	120.2 ± 13.4	-	97.8 ± 4.8	-	94.5 ± 3.0	-	89.0 ± 1.8	-
TG (mg/dl)	18.7 ± 0.6	33.8 ± 4.6	*	34.5 ± 4.8	*	21.7 ± 3.2	-	23.7 ± 2.3	-
TC (mg/dl)	133.5 ± 4.2	107.5 ± 8.6	*	113.7 ± 7.0	*	101.8 ± 3.9	*	103.5 ± 4.9	*
TP (g/dl)	7.7 ± 0.2	7.3 ± 0.2	-	7.4 ± 0.1	-	7.6 ± 0.2	-	7.6 ± 0.2	-
ALP (IU/L)	70.5 ± 10.8	162.2 ± 15.7	*	152.0 ± 15.6	*	111.7 ± 16.6	**	124.8 ± 20.8	*
ALT (IU/L)	42.7 ± 3.0	60.4 ± 2.4	*	48.0 ± 3.3		47.5 ± 3.5	-	49.5 ± 3.6	-
AST (IU/L)	15.8 ± 1.4	17.8 ± 2.2		20.5 ± 4.5		16.8 ± 1.5	-	18.2 ± 2.8	-
BUN (mg/dl)	26.3 ± 1.5	19.5 ± 1.6	*	20.3 ± 1.9	*	20.7 ± 1.6	*	17.3 ± 1.5	*
CRE(mg/dl)	1.2 ± 0.1	1.2 ± 0.1	-	1.2 ± 0.1	-	1.3 ± 0.2	-	1.4 ± 0.2	***
NESA (mEq/l)	0.229 ± 0.038	0.194 ± 0.032	-	0.198 ± 0.031	-	0.301 ± 0.050	-	0.351 ± 0.067	**
Insulin (ng/l)	2.6 ± 0.1	2.9 ± 0.2	-	2.9 ± 0.1	-	2.7 ± 0.0	-	3.9 ± 0.9	-
Adinopectin (mg/ml)	6.6 ± 1.8	10.2 ± 1.2	-	11.7 ± 1.5	*	5.9 ± 1.0	**	5.1 ± 1.1	**
TNFα(ng/mL)	15.3 ± 6.7	15.2 ± 8.7	-	9.2 ± 5.7	*	14.9 ± 7.5	-	15.7 ± 6.0	-
MDA (μmol/l)	0.89 ± 0.05	1.17 ± 0.10	*	0.96 ± 0.04	-	0.92 ± 0.06	-	0.89 ± 0.03	-
SOD (IU/ml)	12.7 ± 5.4	10.01 ± 6.6	-	40.6 ± 4.4	*	53.8 ± 4.8	*	46.7 ± 4.2(5)	*
GSHPx (Miu/ml)	19.1 ± 2.1	19.6 ± 0.6	-	22.7 ± 2.0	-	24.2 ± 2.7	-	23.6 ± 1.9	-
LDH (IU/l)	119.8 ± 14.4	166.7 ± 24.8	-	217.0 ± 76.9	-	142.5 ± 20.0	-	132.2 ± 20.5	-

Values are presented mean ± SE

*Significantly different ($p<0.05$) from the 0 week values

**Significantly different ($p<0.05$) from the 4 weeks values

***Significantly different ($p<0.05$) from the 6 weeks values

The numbers in parentheses indicate the number of animals examined

DISCUSSION

Obesity is a disorder of energy balance, developed when energy intake exceeds energy expenditure, with the excess stored in adipose tissues. Glucose and lipids are the main sources of energy in most mammals, and their metabolism is influenced by weight gain and obesity related diseases such as diabetes mellitus and hyperlipidemia [8-9,14]. Compared to other species, cats have unique glucose and lipid metabolism [15]. The lack of hexokinase IV (glucokinase), one of the rate limiting enzymes that mediate glycolysis in the liver, prevents processing of blood glucose at high concentration, which subsequently accumulates as triglyceride in adipose tissues [16]. Furthermore, the expression levels of mRNA associated with insulin signaling pathway in insulin-responsive tissues were found to be lower in cats [17]. Adiponectin concentration was also found to be lower in cats at normal state as well as with weight gain [17,18] compared to dogs. Together, they suggest that cats inherently have lower ability to process glucose, and are predisposed to obesity and insulin resistance.

Our subjects acutely increased their body condition score to 4.2 and 4.3, in 2, 4 weeks of high-fat diet feeding, respectively, which is generally considered “overweight” in the 5-0 point BCS scale. Significant changes as compared to pre-weight gain values were noted in adiponectin and TNFα during the weight-gain induction phase, and their changes were inversely related. At week 4, the highest peak of adiponectin level was accompanied by the lowest point of TNFα, then showed decreasing and increasing trends, respectively, as the weight reduced (6, 8 weeks). Concomitantly, significant elevations in TG and ALT were also noted with weight gain, although the values weren’t high enough to reach the levels of hyperlipidemia and high ALT set by the new MS diagnosis criteria [19] or the hypertriglyceridemia levels used as the common signs of obesity. Increase in plasma TG levels with weight gain was associated with general elevations ALP, ALT, and AST and may indicate hepatic lipid accumulation as reported previously [20]. Since the identification of the hormone, leptin [21], adipose tissue has become recognized as an important secretory and endocrine organ that actively releases substances, “adipokines” involved in a wide array of physiological processes including glucose and lipid homeostasis, blood pressure, body weight regulations, and immune functions. Substantial evidences suggest the dysregulated synthesis of “harmful” adipokines, such TNFα [22], IL-6 (interleukin-6), and of “beneficial” adipokines, such as adiponectin [23] and leptin [24] associated with obesity, is involved in the development of metabolic syndrome.

Among many secreted adipokines, adiponectin, is of particular interest, since it is involved in glucose and lipid metabolism and exerts direct effects on vasculatures, thus influences the metabolic health of obese individuals [25]. It is mainly secreted by adipocytes, but unlike other adipokines, its secretion and circulating levels are inversely proportional to body fat mass [26]. It modulates the expression of fatty acid transport proteins in liver and skeletal muscle and stimulates fatty oxidation and glucose utilization via activation of AMP Activated Protein Kinase (AMPK) [27]. It also exerts anti-inflammatory actions via inhibition of macrophage activity, and C - reactive protein (CRP), TNFα production and action. Adiponectin was also shown to inhibit TNFα-induced surface expression of adhesion molecules and monocyte adhesion to the epithelium *in vitro*. It is well established that

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plasma adiponectin level is significantly decreased in obese and insulin resistant Type 2 diabetic patients. Furthermore, there were decreased plasma levels in human patients with coronary artery disease

Conversely, adipose expression and circulating levels of TNFα have been positively correlated with adiposity, insulin resistance, and arthrosclerosis in human and rodents. In adipocytes, TNFα interferes with the free fatty acid uptake and lipogenesis, directly altering energy homeostasis. It interferes with insulin signaling, causes endothelial activation and stimulates adhesion molecule synthesis and adhesion to the endothelium. In adipose and liver tissue, it is thought to antagonize the actions of adiponectin, increasing fatty acid oxidation. Many evidences suggest the role of TNFα in the reduction of adiponectin expression and synthesis in obesity. Our study results were in concordance with the previous studies, showing the mutual antagonizing effects of adiponectin and TNFα [28-30]. At the same time, our results showed initial elevation in adiponectin and subsequent decline in TNFα, which may be in response to initial increase in adiposity and adipocyte maturity [31,32], only seen in an early phase of weight gain.

Increase in oxidative stress in adipose tissue leads to dysregulated production of adipokines, which in turn, causes the development of Metabolic Syndrome (MS). MDA is one of the byproducts of lipid peroxidation by Reactive Oxygen Species (ROS) [33], and significant elevation was noted during the acute weight-gain phase (2 weeks) in this study. Superoxide dismutase catalyzes the first step of enzymatic antioxidant pathway against ROS. Elevation in this reaction product reflects body's response against free-radical reactions [34]. Our results showed an early elevation of MDA (2 weeks), and relatively delayed elevation of SOD activities in 4-week-group, and its continued elevation into the weight reduction period (6-week, 8-week groups). It may suggest the presence of oxidative stress in an early phase of weight gain due to lipid peroxidation and the body's immediate protective function against increased oxidative stress.

Together, our results suggest that acute weight gain and high BCS in cats may not necessarily be pathological as long as adiponectin and anti-oxidant protection of the body are in effect. At an early phase of acute weight gain, body's protection against pro-inflammatory and oxidative effects of adiposity remain functional, keeping overweight individuals metabolically healthy even at high BCS. Previous studies suggest the significance of adipose depot distribution (subcutaneous vs visceral) and adipocyte size (small vs. large) and age (immature vs. mature) in adiponectin synthesis, secretion [23,35], and metabolic health.

In our study, adiponectin concentration was detected to be its highest at the highest BCS of 4.3, most likely due to the simple increase in the number of adipocytes and adipocyte maturity during the initial weight gain. Furthermore, the increased activity of SOD, the antioxidant enzyme, followed the elevation in MDA, and maintained its significantly high activity level as the MDA concentration continuously dropped throughout the weight loss process. This may indicate SOD's anti-oxidative response to lipid peroxidation represented by elevation of MDA.

This preliminary study has several limitations. First of all, this study was conducted on small number of samples. Also, there is no established reference values for feline adiponectin, TNF-α, SOD, and MDA, and the tests used to measure such parameters were not officially validated for use in cats. Therefore, the obtained values are used for comparison among various stages of weight change (relative values). Furthermore, the observation was only made at experimental acute weight changes in cats over an 8-week period and the maximum mean body weight change of 23%, and results may not necessarily reflect metabolic changes observed in chronic weight gain or in naturally-occurring weight gain in cats as presented in the study that followed 12 month-weight gain in cats [36]. Rather, this study shows short-term changes observed in acute weight gain and reduction. Also changes in adipose depot distribution and adipocyte size in correlation with BCS and physiological changes were not compared. More refined quantitative studies employing direct measurement of adipocytes, BIA [35,37], dual energy X-ray absorptiometry [38] or special calculations to measure SAT and VAT volumes [39] on increased number of samples should be performed in the future. In the future, the correlation among the above-mentioned parameters, duration of the overweight status, distribution of adipose depot, and adipocyte types in cats should be elucidated to further support our conclusion.

CONCLUSION

Acute weight gain and acute weight loss were experimentally induced in healthy cats. Significant elevations associated with weight gain were seen in TG, ALP, ALT, AST, adiponectin, MDA. Highest BCS was associated with the highest values of TG, AST, adiponectin, and with the lowest value of TNFα. Increase in SOD first appeared at 4 weeks, then reached its highest activity level at 6 weeks, then maintained its elevated level through 8 weeks. These results suggest that acute weight gain and high BCS in cats may not necessarily be pathological as long as adiponectin and anti-oxidant protection of the body are in effect. At an early phase of acute weight gain, body's protection against pro-inflammatory and oxidative effects of adiposity remain functional, keeping overweight individuals metabolically healthy even at high BCS.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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