Changes in glucose tolerance and insulin secretion in a cohort of cats with chronic obesity

Ruchita P. Ahuja, Jon M. Fletcher, L. Abbigail Granger, Chin-Chi Liu, Bruna Miessler, Mark A. Mitchell

Abstract

Obesity, which is the most common spontaneous nutritional disorder in cats, is a known risk factor for the development of diabetes mellitus and has been linked to insulin resistance, hyperinsulinemia, and altered adipose-derived hormone secretion in cats. The objective of this study was to monitor and report changes in the results of serial intravenous glucose tolerance testing (IVGTT) and other metabolic parameters in 4 obese cats over a 4-year period. Serial IVGTT, insulin sensitivity indices, adipokine concentrations, and lipid profiles were evaluated. All cats had IVGTT changes consistent with impaired glucose tolerance and altered insulin secretory patterns during the 4-year study period. There was no significant increase in the fasting blood glucose or insulin concentrations and no changes in the insulin sensitivity indices evaluated. The mean adiponectin concentration decreased significantly over time, but there was no significant increase in the leptin concentration and no changes were observed in lipid profiles. Although IVGTT can be used to document early and/or mild impairment of glucose tolerance and changes in insulin secretory pattern, this test cannot be easily or readily carried out on client-owned cats in most clinical settings. More work needs to be done to establish reliable, convenient methods for earlier identification of cats at risk of developing clinical diabetes mellitus.

Résumé

L'obésité, qui est le désordre nutritionnel spontané le plus fréquent chez les chats, est un facteur de risque connu pour le développement du diabète mellitus et a été associé à une résistance à l'insuline, à de l'hyperinsulinémie et à une sécrétion altérée d'hormone dérivée du tissu adipeux chez les chats. L'objectif de cette étude était de surveiller et rapporter les changements dans les résultats de tests de tolérance au glucose intraveineux en série (IVGTT) et autres paramètres métaboliques chez quatre chats obèses sur une période de 4 ans. Des IVGTT en série, les indices de sensibilité à l'insuline, les concentrations d'adipokines et les profils lipidiques ont été évalués. Tous les chats avaient des changements d'IVGTT compatibles avec une tolérance réduite au glucose et des patrons de sécrétion d'insuline altérés durant la période d'étude de 4 ans. Il n'y avait pas d'augmentation significative des concentrations de glucose sanguin ou d'insuline à jeun et aucun changement dans les indices de sensibilité à l'insuline évalués. La concentration moyenne d'adiponectine a diminué de manière significative en fonction du temps, mais il n'y avait pas d'augmentation significative de la concentration de leptine et aucun changement n'a été observé dans les profils lipidiques. Bien que l'IVGTT peut être utilisé pour documenter une diminution naissante et/ou légère de la tolérance au glucose et des changements dans le patron de sécrétion d'insuline, ce test ne peut pas être réalisé facilement ou rapidement sur des chats de clients dans la plupart des milieux de pratique. Plus de travail doit être fait pour établir des méthodes fiables et pratiques pour une identification plus précoce des chats à risque de développer un diabète mellitus.

(Traduit par Docteur Serge Messier)

Introduction

Obesity is the most common spontaneous nutritional disorder of domestic cats, with approximately 35 to 50% of cats classified as being overweight or obese (1–5). Contributing factors include a sedentary lifestyle, commercial diet formulations, excessive caloric and carbohydrate intake, and unique glucose and lipid metabolism (1,3). Feline obesity and the associated pathologic sequelae impact numerous body systems and increase the risk of developing chronic diseases (1,6,7).

It is well-known that weight gain and obesity in cats can lead to impaired glucose tolerance, decreased insulin sensitivity (8,9), and increased risk for development of clinical diabetes mellitus (DM) (6,7). This risk increases with age and progressive weight gain (10) and subsequent weight loss can result in improvements in insulin sensitivity and glucose tolerance (11). Feline diabetes mellitus has multiple parallels with Type 2 diabetes mellitus (T2DM) in humans and, as a result, cats are considered a useful model for the study of human obesity and T2DM (2,12,13).

To the authors' knowledge, this is the first study to report changes in intravenous glucose tolerance testing (IVGTT), insulin sensitivity indices, lipid profiles, and adipokine concentrations in a cohort of obese cats over a period of 4 y. The authors postulated that chronic obesity would be associated with alterations in the IVGTT consistent

Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, Skip Bertman Drive, Baton Rouge, Louisiana 70803, USA.

Address all correspondence to Dr. Jon M. Fletcher; telephone: (614) 368-2600; email: jon.fletcher@medvet.com

Dr. Fletcher's current address is MedVet, 350 East Wilson Bridge Road, Worthington, Ohio 43085, USA.

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with impaired glucose tolerance, insulin resistance, and abnormal insulin secretion. In addition, the authors expected that the adipokine concentrations and lipid profiles would be consistent with those previously reported in obese cats (14).

Materials and methods

Four adult, obese, purpose-bred, domestic shorthair cats with body condition scores (BCSs) ranging from 7/9 to 9/9 on a 9-point scale were included in this study. All cats were neutered males with a mean age of 5 y (range: 2 to 9 y) at the beginning of the study. This study included data from the baseline evaluation of 2 earlier unpublished studies (baseline and 2 y) combined with a single prospective evaluation conducted 4 y after the baseline evaluation. Data collected during all evaluations included body weight, subcutaneous fat percentage, IVGTT results, lipid profiles, and serum adiponectin and leptin concentrations.

All cats were group-housed, fed a commercial laboratory diet (LabDiet 5003 Laboratory Feline Diet; LabSupply, Northlake, Texas, USA) *ad libitum* and had naturally occurring obesity associated with excessive caloric intake and a sedentary lifestyle. Prior to each evaluation, all cats were deemed to be otherwise healthy based on a normal physical examination, complete blood (cell) count, and serum biochemistry profile.

All cats received intramuscular sedation with dexmedetomidine [0.002 mg/kg body weight (BW)], butorphanol (0.2 mg/kg BW), and ketamine (5 mg/kg BW) to achieve immobilization for a computed tomography (CT) scan and intravenous catheter placement. All studies were approved by the Louisiana State University Institutional Animal Care and Use Committee and carried out in a facility accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC).

The body fat percentage was determined by analysis of whole body CT, which has been validated in cats (15). Cats were positioned in left lateral recumbency for the CT scan and transverse 0.625-mm helical CT images were obtained of each cat from the nasal planum to the tip of the tail using a 16-slice scanner (GE Lightspeed; GE Medical Systems, Milwaukee, Wisconsin, USA). Images were constructed into a standard algorithm and analyzed using an open-source imaging software program, 3D Slicer 4.1.1. The volume of tissue within each cat containing adipose tissue density was semi-automatically segmented from remaining tissues using threshold values of −150 to −50 HU. The fat percentage was calculated as the ratio of the fat volume to the combined total of adipose tissue and nonadipose tissue volumes, excluding any gas.

At least 12 h before conducting IVGTT, cats were sedated for placement of intravenous catheters in the jugular and cephalic veins for blood sampling and glucose administration, respectively. Cats were fasted for 12 to 18 h before IVGTT and a hand-held glucometer (AlphaTRAK 2; Zoetis, Parsippany-Troy Hills, New Jersey, USA) previously validated in cats (16) was used to measure blood glucose.

Approximately 1.5 mL of blood was collected into chilled, glass EDTA tubes and remained on ice until refrigerated centrifugation (4°C, 805 × *g*) at the end of each IVGTT. The plasma was frozen in glass tubes and stored at −80°C until analysis. Fasting/baseline (t = 0) blood glucose and plasma insulin concentrations were obtained before administering 1 g/kg BW of 50% glucose solution diluted 1:1 with 0.9% saline. The blood glucose and plasma insulin concentrations were measured at 5, 10, 15, 30, 45, 60, 90, and 120 min after glucose was administered. An IVGTT was considered normal if, at 120 min after glucose administration, the blood glucose was ≤ 10% of the baseline blood glucose (17) and was considered abnormal if it was > 10% of the baseline blood glucose concentration.

Table I. Insulin sensitivity indices and associated calculation.

Index	Calculation
Insulin-to-glucose ratio	fasting insulin (μU/mL) ÷ fasting glucose (mmol/L)
HOMA-IR	[fasting glucose (mmol/L) × fasting insulin (μU/mL)]/22.5
QUICKI	1/[log fasting insulin (μU/mL) + log fasting glucose (mg/dL)]

HOMA-IR — homeostatic model assessment of insulin resistance; QUICKI — quantitative insulin sensitivity check index.

Insulin quantification was done with a commercially available feline insulin enzyme-linked immunosorbent assay (ELISA) (Mercodia, Uppsala, Sweden) previously validated for the detection of feline insulin (18). The ELISAs were conducted according to the manufacturer's protocol and absorbance was read at 450 nm with an automated ELISA plate reader (Epoch; BioTek, Winooski, Vermont, USA). The assay range is 10 to 700 ng/L. Samples that exceeded the assay range were diluted 1:10 with the dilution buffer per the manufacturer's recommendation. The intra- and inter-assay coefficients of variation (CVs) were 5.71 ± 1.68% and 3.31 ± 3.99%, respectively.

A high-sensitivity adiponectin human ELISA (BioVendor, Brno, Czech Republic) was used to quantify adiponectin. This assay has a detection range of 5 to 100 ng/mL and known cross-reactivity with feline adiponectin. It has been previously validated in cats (19) and used in other studies (14,20). All samples were diluted 1:30 prior to analysis according to the manufacturer's recommendation. The intra- and inter-assay CVs were 6.48 ± 2.91% and 8.11 ± 7.07%, respectively. A validated feline leptin ELISA Kit (MyBioSource, San Diego, California, USA) was used to quantify leptin (21). The assay detection range is 0.5 to 16 ng/mL. The intra- and inter-assay CVs were 12.22 ± 5.18% and 10.16 ± 8.72%, respectively. The lipid profiles [cholesterol, triglyceride, and high-density lipoprotein (HDL)] were conducted in a commercial research laboratory (IDEXX BioResearch Laboratory, Westbrook, Maine, USA).

Insulin sensitivity indices evaluated included the insulin-to-glucose ratio (I:G), homeostatic model assessment for insulin resistance (HOMA-IR), and the quantitative insulin sensitivity check index (QUICKI) (Table I). The blood glucose and plasma insulin concentrations from the fasting/baseline sample of the IVGTT were used to calculate the insulin sensitivity indices (22).

In order to assess the change in these parameters over time, the data obtained during the prospective evaluation were compared to historical data that were collected 2 and 4 y ago. The distributions of the data were evaluated using the Shapiro-Wilk test, skewness, kurtosis, and q-q plots. Data that were normally distributed are reported as mean ± SD, whereas data that were not normally

Table II. Intravenous glucose tolerance test (IVGTT) parameters at baseline, 2 y, and 4 y. Data are reported as median (min-max).

IVGTT parameters	Time (y) 0	2	4
Glucose 0 (mg/dL)	84 (80 to 86)	100 (90 to 115)	96 (87 to 104)
Insulin 0 (ng/L)	9.13 (9.13 to 96.9)	71 (62.3 to 134.1)	109.5 (87.2 to 187)
Glucose 120 (mg/dL)	72 (62 to 138)	186.5 (94 to 233)	233.5 (167 to 381)
Insulin 120 (ng/L)	26.4 (12.6 to 229.3)	590.2[a] (196.5 to 930.2)	728[b] (671.7 to 1442)
Glucose AUC	40 974 (36 618 to 41 613)	52 057 (44 250 to 58 143)	58 632 (47 135 to 66 283)
Insulin AUC	92 011 (24 713 to 108 324)	93 331 (56 518 to 190 752)	87 740 (80 710 to 187 491)

[a] A significant difference between year 2 and baseline ($P = 0.042$).

[b] A significant difference between year 4 and baseline ($P = 0.022$).

AUC — area under the curve.

Table III. Insulin sensitivity indices at baseline, 2 y, and 4 y. Data are reported as median (min-max).

Insulin sensitivity index	Time (y) 0	2	4
Insulin-to-glucose ratio[a]	0.06 (0.06 to 0.59)	0.36 (0.32 to 0.97)	0.6 (0.53 to 0.97)
HOMA-IR[a]	0.05 (0.05 to 0.59)	0.57 (0.40 to 0.86)	0.76 (0.54 to 1.35)
QUICKI[b]	0.74 (0.42 to 0.75)	0.42 (0.39 to 0.45)	0.40 (0.36 to 0.43)

[a] The higher the value, the lower the insulin sensitivity.

[b] The lower the value, the lower the insulin sensitivity.

HOMA-IR — homeostatic model assessment of insulin resistance; QUICKI — quantitative insulin sensitivity check index.

Table IV. Adipokines and lipid profile results at baseline, 2 y, and 4 y. Data are reported as mean ± SD.

	Time (y) 0	2	4
Adiponectin (ng/mL)	693.6 ± 31.5	359.8 ± 73.3[a]	560.5 ± 52.4[b,c]
Leptin (ng/mL)	2.83 ± 0.32	4.35 ± 1.81	3.4 ± 1.94
Cholesterol (mg/dL)	109 ± 33	121 ± 15	126 ± 11
Triglyceride (mg/dL)	59 ± 11	45 ± 20	64 ± 23
HDL (mg/dL)	116 ± 28	105 ± 8	112 ± 16

[a] A significant difference between year 2 and baseline ($P = 0.003$).

[b] A significant difference between year 4 and baseline ($P = 0.028$).

[c] A significant difference between year 4 and year 2 ($P = 0.018$).

HDL — High-density lipoprotein.

distributed are reported as median (min-max). Data that were not normally distributed resumed normal distribution following log transformation and were analyzed with parametric tests. The trapezoid rule was used to compute the area under the curve (AUC) for each adjacent pair of points defining a curve that was created by nonlinear regression (GraphPad Prism 9; GraphPad Software, San Diego, California, USA).

Repeated measures analysis of variance (ANOVA) were used to evaluate each of the outcome variables (body weight, fat percentage, fasting blood glucose and insulin, blood glucose and insulin during IVGTT, AUC glucose, AUC insulin, I:G, HOMA-IR, QUICKI, adinopectin, leptin, cholesterol, triglyceride, and HDL) over time. Mauchly's test was used to test for sphericity. If sphericity was violated, the Greenhouse-Geisser method was used to interpret the results. If significance was found, the Bonferroni test was used to identify the difference between study years. SPSS 23.0 (IBM Statistics, Armonk, New York, USA) was used to analyze the data. A $P \leq 0.05$ was used to determine statistical significance.

Results

Four adult, obese, purpose-bred, domestic shorthair cats with body condition scores (BCSs) ranging from 7/9 to 9/9 on a 9-point scale were included in this study. All cats were neutered males with a mean age at the beginning of the study of 5 y (2 to 9 y). The mean body weights of the cats were 4.98 kg ± 0.62 1 y before the baseline evaluation, 5.78 kg ± 0.47 at baseline, 6.34 kg ± 0.61 at 2 y, and 6.94 kg ± 0.78 at 4 y. The median fat percentages were 32% (range: 25 to 45%), 34% (range: 29 to 44%), and 33% (range: 31 to 52%) at baseline, 2 y, and 4 y, respectively. There was no significant change in

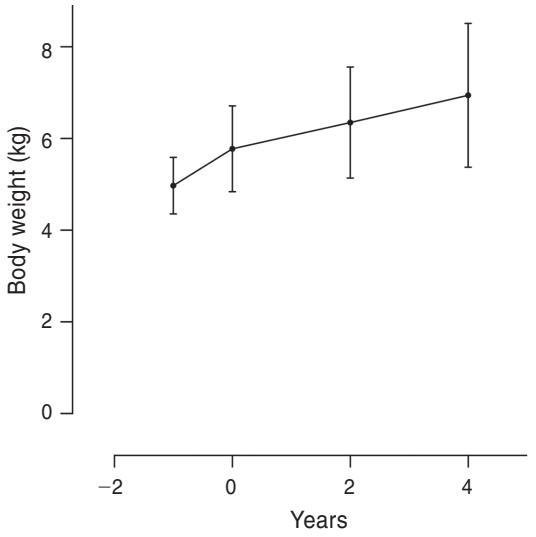

Figure 1. Body weight of cats 1 y before and during the study period. Results are expressed as mean ± SD.

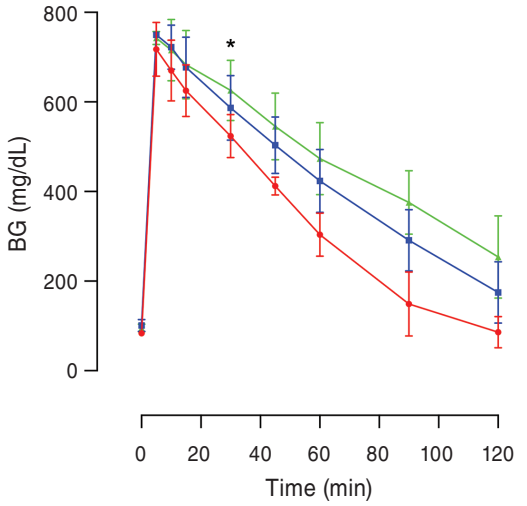

Figure 2. Blood glucose concentrations (n = 4) during the intravenous glucose tolerance tests (IVGTTs) at baseline (●), 2 y (■), and 4 y (▲). Results are expressed as mean ± SD.

*** $P < 0.05$ comparing changes in mean concentration between years.**

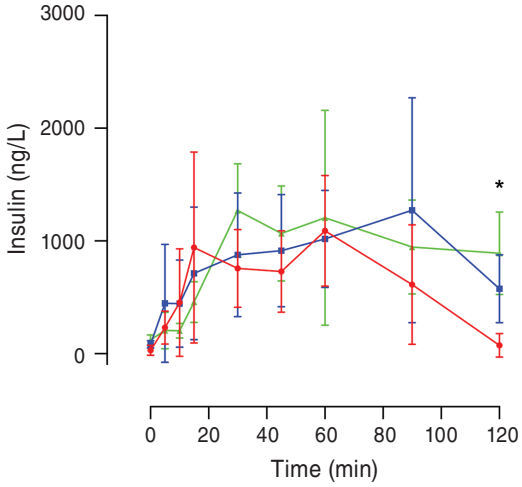

Figure 3. Plasma insulin concentrations (n = 4) during the intravenous glucose tolerance tests (IVGTTs) at baseline (●), 2 y (■), and 4 y (▲). Results are expressed as mean ± SD.

*** $P < 0.05$ comparing changes in mean concentration between years.**

body weight (F = 2.98, P = 0.09) or fat percentage (F = 0.83, P = 0.48) during the study period.

There was no significant increase in the fasting blood glucose (F = 3.5, P = 0.1). There was a significant increase in the blood glucose concentration at 30 min (F = 37.19, $P < 0.001$). Although the increase in the blood glucose concentration at 120 min did not reach significance (F = 4.15, P = 0.07), all cats failed the IVGTT, i.e., did not return to ≤ + 10% baseline blood glucose, by the end of the 4-year study period. Although there was an increase in the fasting insulin concentration (F = 8.71, P = 0.06), this increase was not significant. The increase in the insulin concentration at 120 min in years 2 and 4 was significant (F = 30.05, P = 0.001) (Table II).

An increase in the total AUC for blood glucose (F = 9.05, P = 0.028) was observed, but the pairwise comparison revealed that the increases that occurred in years 2 (P = 0.21) and 4 (P = 0.08) were not significant. The increase in the AUC 60 for blood glucose (F = 21.65, P = 0.014) occurred between baseline and year 4 (P = 0.04). Total AUC (F = 1.28, P = 0.31) and AUC 60 for insulin (F = 0.42, P = 0.49) did not increase over time. The observed increase in the I:G (F = 7.87, P = 0.062) and HOMA-IR (F = 9.24, P = 0.051) and decrease in the QUICKI (F = 9.3, P = 0.053) did not reach significance (Table III).

The adiponectin concentration decreased in this cohort of cats during the study period (F = 85.51, $P < 0.001$), but there was no significant increase in the leptin concentration (F = 0.85, P = 0.47). Cholesterol (F = 1.02, P = 0.42), triglyceride (F = 4.14, P = 0.61), and HDL (F = 0.57, P = 0.59) concentrations were also not observed to change over time (Table IV).

Discussion

To the authors' knowledge, this is the first study to evaluate the effects of chronic obesity in cats for a period of time > 12 mo. This cohort of cats had documented weight gain in the year before the first evaluation, with continued weight gain throughout the study period (Figure 1). At the time of the baseline evaluation, all cats were considered to be obese, based on physical examination, body weight, body condition scoring, and a body fat percentage > 25%, which would be considered obese when compared to the previously published studies assessing body composition by dual energy X-ray absorptiometry (DEXA) scan (23,24). The location of the body fat, i.e., subcutaneous *versus* intra-abdominal, was not differentiated in this study because it has been previously suggested that distribution and location of body fat do not play a major role in the degree of associated insulin resistance in cats (6,25).

Intravenous glucose tolerance testing (IVGTT) is considered to be a sensitive test for assessing insulin resistance (IR), alterations in insulin secretion, and early signs of beta cell dysfunction (17,26). In this cohort of cats, the IVGTT was normal at baseline and abnormal at the 2- and 4-year evaluation (Figure 2). The abnormal IVGTT results and increased glucose AUC observed in this study support

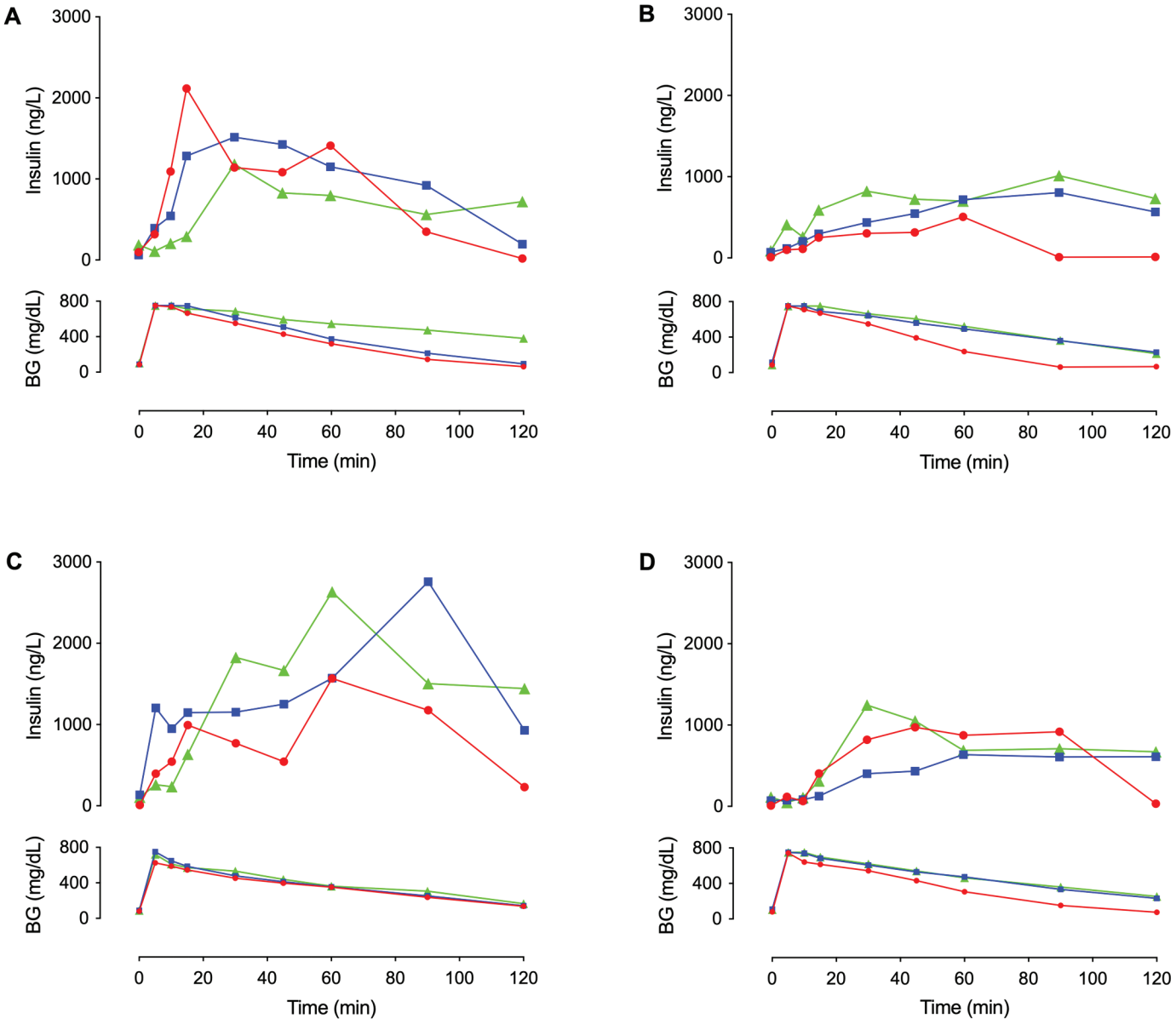

Figure 4. Intravenous glucose tolerance test (IVGTT) results in individual cats (A to D). Blood glucose and plasma insulin concentrations during the IVGTT at baseline (●), 2 y (■), and 4 y (▲). The labeling of cats (A to D) is consistent in all figures.

impaired glucose tolerance. A biphasic insulin secretory pattern, characterized by an early first phase, followed by a more gradual and sustained second phase of insulin release, has been documented with IVGTT in humans and in healthy, lean cats (2,26,27) and was observed at the baseline evaluation in these cats (Figure 3).

Obesity and experimental induction of insulin resistance (IR) in healthy cats have been shown to result in an altered insulin secretory pattern, most notably a progressively diminishing first phase and an exaggerated second phase (9,17,26). This was most evident in year 2 in this cohort of cats (Figure 3). In year 4, peak insulin secretion was delayed, the first phase was not distinguishable, and high insulin concentrations were sustained through to the end of the IVGTT (Figure 3).

Increased fasting insulin and exaggerated insulin secretion in response to a glucose load are consistent with a compensatory increase in insulin secretion in response to impaired glucose tolerance and IR (9,17,26). Although the increase in fasting insulin did not reach significance in these cats, the increase in the insulin concentration at the end of IVGTT (120 min after glucose administration) does support a compensatory increase in insulin secretion. Hyperinsulinemia, which has been previously documented in obese cats, is suspected to be an early response to IR as the first phase of insulin secretion diminishes (26). As in this study, the appearance of increased insulin secretion during the IVGTT without a significant increase in the insulin AUC has been previously reported and is postulated to be secondary to changes in the overall insulin secretory pattern (17,28).

Independent assessment of the IVGTT in each cat revealed that 3/4 cats had a normal IVGTT at baseline (Figure 4 A, B, D). The 1 cat with an abnormal IVGTT at baseline (Figure 4 C) also

had an abnormal result at 2 and 4 y. This cat also had an altered insulin secretory pattern in years 2 and 4, which was characterized by delayed and exaggerated peak insulin secretion > 60 min (Figure 4 C). Two cats with a normal IVGTT at baseline had an abnormal IVGTT at 2 and 4 y (Figure 4 B, D) and all cats had an abnormal IVGTT at 4 y (Figure 4 A to D).

A biphasic insulin secretory pattern was identifiable in 2 cats (Figure 4 A, C), whereas 2 cats had more gradual and sustained insulin release without an obvious first phase (Figure 4 B, D). One cat in this study had a visible reduction in insulin secretion, as well as a decrease in the insulin AUC at year 4 compared to baseline (Figure 4 A). The authors speculate that beta cell dysfunction played a role in the reduction of insulin secretion. No cats in this study developed overt diabetes mellitus and all cats maintained a fasting blood glucose concentration below the published cutoff of 117 mg/dL (29).

Indices of insulin sensitivity are commonly used in humans for assessing the presence of insulin resistance (30–31). Several of these indices have also been evaluated in cats and found to correlate with the minimal model-derived insulin sensitivity index (22). In this study, we evaluated the I:G, HOMA-IR, and QUICKI. All insulin sensitivity parameters trended in a direction consistent with increasing insulin resistance but did not reach significance. Although the authors suspect that small sample size contributed to the inability to detect a difference in this cohort, substantial variability, and the influence of external factors on the fasting glucose and insulin concentrations limit the usefulness of these assessments in individual cats and small cohorts of cats. The discordance between the IVGTT and indices is likely the result of decreased sensitivity of the indices when compared to the IVGTT.

As in humans, obesity in cats has been associated with decreased adiponectin, increased leptin, and dyslipidemia characterized by hypertriglyceridemia, increased concentrations of non-esterified fatty acids, and increased very-low density lipoproteins (VLDL) (2,25,32–34). All cats in this study had a reduction in the adiponectin concentration, but the leptin concentration did not increase significantly in this cohort during the study period and the concentrations were lower than those previously reported in obese cats (14,21,35). In addition, the lipid profiles were within the reference intervals and did not change during the study period. Potential explanations include small sample size, lack of a significant increase in body weight and body fat percentage during the study period, lower body fat percentage in this cohort compared to the cats in previous studies, use of different methodologies, and a wide range and overlapping published concentrations of leptin in cats (14,21,35).

Small sample size is the most significant limitation of this study. This cohort of cats was studied because they were of known age, developed obesity over a known period of time, and had known backgrounds, including diet and lack of medical issues or administration of medications. Despite the small sample size, significant changes were observed in the IVGTT and insulin secretory pattern. While a male-only cohort is not uncommon in study design, it means that this study has limited application to female cats. Future studies should therefore include a larger cohort of both male and female cats.

Although IVGTT is a sensitive test for assessing insulin resistance (IR), alterations in insulin secretion, and early signs of beta cell dysfunction and for diagnosing impaired glucose tolerance in cats (9,17,26,36–38), it does not allow differentiation of the anatomic location of the IR and is an incomplete assessment of insulin secretion. The hyperinsulinemic-euglycemic clamp method is considered the gold standard for assessing insulin resistance in humans (2,33), but is more challenging and labor-intensive to carry out. In addition, a more complete assessment of the insulin secretory capacity would have been achieved with a hyperglycemic clamp or oral lipid administration, which would also encompass the incretin effect (39). Similar challenges, side effects, and complications would be expected for the oral glucose tolerance test (OGTT) (38) and the usefulness of a test that requires oral administration of lipids would be greatly limited in cats, especially in client-owned animals.

In conclusion, this study used serial intravenous glucose tolerance testing (IVGTT) to document the development of impaired glucose tolerance and changes in the insulin secretory pattern in a cohort of obese cats over a period of 4 y. Although IVGTT can be used to document early and/or mild impairment of glucose tolerance, it cannot be easily or readily carried out in client-owned cats in most clinical settings. In addition, day-to-day variability in fasting glucose and insulin concentrations and the effects of stress hyperglycemia limit the utility of insulin sensitivity indices that use these parameters in cats. More work needs to be done to establish reliable, convenient methods for the earlier identification of cats that are at risk of developing clinical diabetes mellitus.

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