

Veterinary Biometrics and Epidemiology

Assignment 3 – Biometrics and Epidemiology

Due Monday 6 October 2008

Provide an appraisal of the following article using the worksheet attached to this document:

Little C, Gettinby G (2008) Heart failure is common in diabetic cats: findings from a retrospective case-controlled study in first-opinion practice. *Journal of Small Animal Practice* 49, 17 - 25.

Print the worksheet out and write your answers in the spaces provided.

Be sure to address *both* statistical and epidemiological features of the paper in your response.

Heart failure is common in diabetic cats: findings from a retrospective case-controlled study in first-opinion practice

OBJECTIVES: To study the prognosis and cause of death in cats with diabetes mellitus.

METHODS: Twenty consecutive cases of feline diabetes mellitus diagnosed in first-opinion practice were followed. Three control cats, without diabetes, were matched to each case of diabetes; these were also followed.

RESULTS: One Somali cat with diabetes could not be matched, so complete data analysis considered only 19 diabetics and 57 matched controls. Death occurred in 14 of 20 diabetics and 23 of 57 controls although one control cat was eventually lost to follow-up. Heart disease and heart failure led to death in six diabetic cats. One of these was the non-matched Somali; nevertheless, the death rate from heart disease in the diabetics was five of 19 compared with two of 57 in controls. The relative risk of heart failure in diabetic cats was 10.4 times that of the controls; this difference in rates was statistically significant. Survival amongst diabetics was significantly worse than for controls. For the control cats median survival was 718 days after the index visit, whereas for the diabetic cases median survival was 385 days after diagnosis.

CLINICAL SIGNIFICANCE: Heart disease and failure are common in diabetic cats. This observation deserves further attention.

C. J. L. LITTLE AND G. GETTINBY*

Journal of Small Animal Practice (2008)
49, 17–25
DOI: 10.1111/j.1748-5827.2007.00466.x

Barton Veterinary Hospital, 34 New Dover Road,
Canterbury, CT1 3BH Kent

*Department of Statistics and Modelling
Science, University of Strathclyde, Glasgow
G1 1XD

INTRODUCTION

Diabetes mellitus is common in the cat and the prevalence of this condition appears to be increasing (Peterson 1998, Rand and Marshall 2004, Rand and others 2004). The prognosis for cats with diabetes mellitus in first-opinion practice has received little attention in the literature; few data indicate why diabetic cats die. Death in people with diabetes is overwhelmingly because of cardiovascular disease (Grundy and others 1999, Almdal and others 2004, Bell 2004, Bertoni and others 2004, Nichols and others 2004).

Experimental induction of diabetes mellitus in various laboratory mammals also causes cardiovascular disease and heart failure so that the prevalence of cardiac disease and failure in diabetic cats seemed worthy of examination. The purpose of this study was to examine the prognosis and cause of death for a cohort of consecutive cases of feline diabetes mellitus diagnosed in a first-opinion veterinary practice, and to compare these with control cats matched for age, breed and sex.

MATERIALS AND METHODS

Selection of cases

The computer records of Barton Veterinary Hospital (BVH) were searched for all cases of feline diabetes first diagnosed during a six year period between June 1999 and June 2005. Searching was achieved by identifying all cats for which a fructosamine assay had been performed, and/or where insulin therapy, or oral hypoglycaemic medication, and/or a diet designed for use with feline diabetes had been dispensed. These raw records were then reviewed in detail to identify cases, which were confirmed as diabetic based on compatible clinical signs, concurrent hyperglycaemia and glycosuria, or concurrent elevated fructosamine levels, or both. These records were further sorted to identify those cases, which had been diagnosed in the first-opinion stream of the practice and treated under our care thereafter.

Selection of controls

For each case of diabetes diagnosed according to these criteria, three matched non-diabetic control cats were sought by the following routine. The date of diagnosis of each diabetic was identified together with their breed, sex and age on that date. The hospital database was searched for matching control cats of the same age (to the nearest year), breed and sex which

had been seen at the hospital, either for a routine vaccination or a new episode of illness, within a maximum of 90 days before or after the date of diagnosis of the index diabetic case. If more than three control cases were found, three control cases were chosen at random.

RESULTS

Diabetic cats

A total of 28 cats with a new diagnosis of diabetes were examined and treated at BVH during the six year period in question. Of these 28 cats, six were excluded from further detailed analysis because their condition was originally diagnosed elsewhere and the cats were referred to our second opinion service and/or their condition was managed at another practice subsequent to the cat being seen at our practice. Another two cats had both diabetes and hyperthyroidism. These cases were also excluded from further analysis. The remaining 20 cats were the subject of this study.

All cats diagnosed as diabetic exhibited marked and persistent hyperglycaemia and glycosuria at the time of diagnosis

as well as compatible clinical signs. The principal clinical signs recorded from these animals were: polydipsia/polyuria (80 per cent), weight loss (75 per cent), polyphagia (65 per cent), depression/lethargy (25 per cent), capricious/variable appetite (15 per cent), dysuria/haematuria (15 per cent) and peripheral neuropathy (10 per cent). Following routine haematology, biochemistry and urinalyses, other laboratory tests were frequently used in the evaluation of these diabetic cats; those tests used most frequently were: fructosamine assays for diagnosis and/or monitoring (in 75 per cent of cases), serial glucose curves (70 per cent of cases) and measurements of thyroid hormone (50 per cent of cases). Systemic arterial blood pressure was not measured in these cats.

The 20 cats consisted of 15 domestic shorthairs (DSH), four domestic longhairs (DLH) and one Somali cat. Males outnumbered females (13:7); all were neutered. Most cats were middle-aged or older at the time of diagnosis (range six to 16 years). Median age at diagnosis was 12 years.

We were unable to find any matching control cats for the male Somali cat (case 16), consequently this cat was excluded

from the case-control study for which only 19 diabetic cats were thus eligible.

Control cats (n=57) consisted of 45 DSH and 12 DLH. The sex ratio of these cats was identical to the diabetic cases (36 males, 21 females) and again all were neutered. Age structure of the control group strongly resembled the age of the cases (range five to 16 years, median 11.5 years).

Treatment and clinical outcomes of the diabetic cases

At the time of writing, of these 20 diabetic cats, 14 were dead and six were still alive. The cause(s) to which death or euthanasia was ascribed are given in Table 1. Of the 14 cats that died, six were caused by heart failure. Details of the clinical and laboratory findings which confirmed the presence of heart failure in these cats are given in Tables 2 and 3.

One cat was euthanased, without treatment, three days after diagnosis (case 15). Most of the cats that were treated eventually received insulin therapy (n=17) and a diet particularly designed for diabetic cats (n=11) (Hills Feline W/D n=6, Hills Feline M/D n=5). However, some of the cats were initially treated with an oral hypoglycaemic agent (glipizide, see

Table 1. Causes of death in the 14 diabetic cats which have died

Cause of death/euthanasia	Numbers	Cases	Details of diagnostic findings	Other information
Heart failure	6/14	2, 4, 7, 10, 13, 16*	See Tables 2 and 3	One died, five euthanased
Chronic renal failure	2/14	17, 18	Azotaemia, cachexia and persistent polyuria In spite of reasonable control of the diabetes, based on fructosamine and plasma glucose monitoring	Two euthanased
Poor diabetic control: "unstable"	2/14	9, 12	Persistent/frequent hyperglycaemia and glycosuria Elevated fructosamine	2 euthanased
Hypoglycaemia with convulsions	1/14	19	Owners persisted with treatment for 17 (case 9) and 16 months (case 12) respectively. Hypoglycaemia. Neurological signs persisted after euglycaemia was achieved	One (12) treated with glipizide only Other (9) treated with PZI insulin once a day Euthanased
Owner requested euthanasia without treatment	1/14	15	—	Owner, a doctor, was managing this cat's diabetes herself Euthanased (three days after diagnosis)
Profound anaemia	1/14	14	Investigation not permitted by owner	Euthanased
Sudden death	1/14	8	Glycaemic control being attempted with glipizide	Died

*This cat was a male Somali and no matched controls were available. It was omitted from the case-control analyses

Table 2. History and diagnostic findings used to diagnose heart failure in six diabetic cats

Case	Interval between diagnosis of diabetes and development of heart failure	History at time of diagnosis of heart failure	Physical examination. Findings at time of diagnosis of heart failure	Plasma [T4]	Radiography	ECG	Echo	Pleural effusion	Ascites	Outcome
2	10 weeks	Inappetence, weight loss, dyspnoea	T 38°C, HR 164 bpm, RR 80 bpm, dyspnoea, hyperpnoea, inspiratory crackles on auscultation	21.6 nmol/l	Patchy increase in pulmonary density, air bronchograms, cardiomegaly, VHS 11.5	Sinus rhythm, latterly frequent, ventricular premature complexes	+ (see Table 3)	Scant effusion after diabetes had been present for 12 months, severe effusion three weeks later	-	Euthanased 10 months after diagnosis of heart failure
10	30 months	Dull, abdominal swelling, anorexia	T 37.4°C, HR 120 bpm, RR 40 bpm, mild dehydration, cold pinnae and feet	Not done	Not done	Sinus bradycardia	+ (see Table 3)	250 ml, modified transudate, TP 38 g/l, Trig 0.47 mmol/l, Chol 2.2 mmol/l, 'Not consistent with chyle'	Large volume, modified transudate TP 34 g/l	Euthanased one week after diagnosis of heart failure
7	16 months	Dullness, anorexia	T 38.5°C, HR 140 bpm, RR 60 bpm, intermittent tachydysrhythmia	Not done	Pleural effusion	Not permitted	+ (see Table 3)	50 ml pure transudate, TP 21 g/l Trig 0.51 mmol/l, Chol 0.76 mmol/l	-	Euthanased three weeks after heart failure diagnosed
13	Seven months	Inappetence, open-mouth breathing	HR 168 bpm, RR 60 bpm, loud breath sounds on auscultation, intractable	22.0 nmol/l	Cardiomegaly VHS 9.1 (after thoracocentesis)	Not done	+ (see Table 3)	220 ml, bloodstained	-	Died 10 days after heart failure diagnosed
4	12 months	Lethargy, weight loss, abdominal swelling	T 38.9°C, irregular heart, HR ~200 bpm, abdominal effort to breathe, fluid thrill in abdomen	Not done	Cardiomegaly VHS 9.3	Atrial fibrillation with RBBB pattern	Not done	Absent	Modified transudate TP 42 g/l	Euthanased one day after heart failure diagnosed
16*	Five weeks	Dull, PUPD, increased respiratory effort	T 38.4°C, HR 120, RR 40 bpm, bradycardia worsened over 48 hours	12.9 nmol/l	Pleural fluid	Third degree heart block: ventricular rate 70 bpm	+ (see Table 3)	130 ml cloudy fluid protein, Trig and Chol content not measured	-	Euthanased three days after heart failure diagnosed

*This cat was not used in the case control study
 ECG Electrocardiography, Echo Echocardiography, T body temperature, HR Heart rate in beats per minute (bpm), RR Respiratory rate in breaths per minute (bpm), VHS Vertebral Heart Sum (Lister and Buchanan 2000), TP Total protein, Trig Triglyceride, Chol Cholesterol, RBBB Right bundle branch block, PUPD Polyuria and polydipsia

Table 3. Echocardiographic findings, diabetic cats

Case	LVED (mm)	LVES (mm)	FWED (mm)	FWES (mm)	IVSED (mm)	IVSES (mm)	Fractional shortening (per cent)	MVI	TVI	AI	PVI	Ao (mm)	LA (mm)	LA : Ao	Other findings	Alive or dead	
2	20	11.6	8.1	12.3	7.8	8.8	35	+++	-	-	-	8.6	22.5	2.6:1	Pleural effusion	Dead	
10	13	6.3	7.7	8.7	7.3	8.1	52	-	+	-	-	9.5	Enlarged 9.8	Enlarged 1.03:1	Pleural effusion, pericardial thickening, ascites	Dead	
7	17.6	8.7	7.4	10.1	5.5	8.0	51	+	-	-	-	1.1	25.2	2.3:1	Pleural effusion	Dead	
13	15	10	5	6	4	7	33	NR	NR	NR	NR	Not measured	Enlarged but not measured	NR	"Smoke" in left atrium, pleural effusion	Dead	
4	Not done, not permitted														Cardiomegaly, atrial fibrillation with RBBB pattern, ascites	Dead	
16*	17.1	9.9	4.8	7.9	4.8	6.3	42	+	+++	-	-	-	-	-	Third degree heart block, pleural effusion	Dead	
Reference values																	
Jacobs and Knight (1985)	12-19.8	5.2-10.8	2.2-4.4	5.4-8.1	2.2-4.0	4.7-7.0	39-61					7.2-11.9	9.3-15.1	0.95-1.65			
Pipers and others (1979)	11.2-21.8	5.2-10.8	3.2-5.6		2.8-6.0		23-56					4.0-11.8	4.5-11.2				
Sisson and others (1991)	10.8-21.4	4.0-11.2	2.5-6.0	4.3-9.8	3.0-6.0	4.0-9.0	40-66.7	-	-	-	-	6.0-12.1	7.0-17.0	0.88-1.79			

*This cat was not included in the case control study

LVED Left ventricular diameter, end diastole, LVES Left ventricular diameter end systole, FWED Left ventricular free wall thickness, end diastole, FWES Left ventricular free wall, end systole, IVSED Interventricular septum end diastole, IVSES Interventricular septum end systole, MVI Mitral valve incompetence, TVI Tricuspid valve incompetence, AI Aortic valve incompetence, PVI Pulmonic valve incompetence, Ao Aortic diameter, LA Left atrial diameter, La : Ao Ratio of left atrial to aortic diameters, "Thick" or "Enlarged": exceeds all reference values listed, NR Not recorded

below). Insulin therapy most frequently consisted of Lente insulin given twice daily. Insulin dose was adjusted based on plasma glucose curves and fructosamine assays in most cases. Maximum dose of insulin recorded was six units twice daily. Of the cats treated with insulin, four of 17 had insulin therapy withdrawn at some time because the requirement for exogenous insulin therapy eventually disappeared; in three of these cases insulin therapy had to be reinstated some months later.

Glipizide (2.5 to 5.0 mg twice a day) was used initially to treat several cats (n=6) but this resulted in poor glycaemic control in five cases, one of which died suddenly (case 8; Table 1). One cat treated in this way developed diabetic hyperosmolar syndrome (case 3) and another developed severe dehydration, azotaemia and ketoacidosis with hypokalaemia (case 11). Four of these cats initially treated with glipizide were eventually treated with insulin. One cat receiving glipizide exhibited fair control of glycaemia for many months, but eventually, because of unstable blood glucose levels and ongoing clinical signs, this cat was euthanased at the owner's request (case 12; Table 1).

Control cats' clinical outcomes

At the time of writing, 23 of the control cats are known to have died and 33 are

known to be still alive. One of these control cats has been lost to follow-up. Of the 23 deaths in this group, seven were attributed to chronic renal disease, four to neoplasia (mammary adenocarcinoma, squamous cell carcinoma of the mouth, salivary gland carcinoma and undiagnosed neoplasm of the lower bowel), four were attributed to hyperthyroidism (in two cases complicated by other conditions; cholangiohepatitis and recurrent idiopathic cystitis) and two to heart failure. For the cats where heart failure was diagnosed, details of the clinical and laboratory findings, which confirmed the presence of heart failure in these cats are given in Table 4. Various other abnormalities were listed as the immediate cause of death or euthanasia in one control case each (road traffic accident, feline immunodeficiency virus, chronic abscess, undifferentiated anaemia with hypoalbuminaemia). In two control cases that were euthanased, no diagnosis was recorded. Neither of these cats was showing signs attributable to cardiovascular or respiratory disease.

Data management and statistical analyses

Information on each of the 19 eligible cases and their three matched controls

was classified according to heart disease (presence or absence), survival outcome (alive or dead at the end of the study), survival time since diagnosis (days), sex (male or female neuter), age (years) and breed (DSH or DLH).

Cases and controls were compared using binary logistic regression to identify which factors were associated with (i) the risk of heart disease and (ii) the risk of mortality during the course of the study. Factors found not to be significant were retained as forced covariates within the model after investigating the stability of fitting other models with and without each factor. Two-factor interactions between fitted factors were examined. Results consisting of the odds ratios, 95 per cent confidence intervals (CI) and statistical significance of the final models were obtained.

In addition, survival analysis and the Weibull distribution model were used to identify those factors and their 95 per cent CI which significantly influenced how long case and control cats lived following recruitment. As some cats were still alive following the end of the study, the data were adjusted for censored observations.

Data were summarised using classification tables and a box plot used to compare the distribution of life times of cases and controls.

Table 4. History and diagnostic findings used to diagnose heart failure in two non-diabetic control cats

Controls	History	Physical examination findings	Radiography	ECG	Echo	Pleural effusion	Ascites	Outcome
Control 2b	Inappetence, sudden onset dyspnoea	T 37.4°C, HR 185 bpm, RR 74 brpm, grade III/VI systolic heart murmur, crackles heard on pulmonary auscultation, normal percussion Pulmonary oedema fluid expelled through mouth, cardiopulmonary massage required, given intravenous frusemide and placed in an oxygen cage Improved	Diffuse increased lung density with air bronchograms Cardiac silhouette partially obscured but cardiomegaly VHS 8-7	Not done	Not done	Absent	Absent	Died four days after heart failure diagnosed
Control 14b	Weight loss, abdominal swelling, blindness	T 38.4°C, HR 120 bpm, Grade II/VI systolic heart murmur, Retinal haemorrhages, Fluid thrill in abdomen	Not permitted	Not permitted	Not permitted	Not permitted	Modified transudate TP 40 g/l	Euthanased two months after heart failure diagnosed

ECG Electrocardiography, Echo Echocardiography, T Body temperature, HR Heart rate in beats per minute (bpm), RR Respiratory rate in breaths per minute (brpm), VHS Vertebral Heart Sum (Lister and Buchanan 2000)

Review worksheet

Title

Authors

Is the contribution to knowledge new and substantial?

Recommendation

Accept article as is.

Accept article with minor modifications (details below).

Accept article with revision (details below).

Accept article with major revision (details below) and re-review.

Reject article – unsuitable for publication (details below).

Comments:

Description of the evidence

What relationship was evaluated?

What was the hypothesis?

What was the study design?

What were the exposure variables?

What was the outcome variable(s)?

What was the source population?

What was the eligible population?

What was the study population?

What was the time frame of interest?

What was the geographic area of interest?

What were the main results of the study?

Internal validity

Does the evidence support a causal relationship or just an association between outcome and exposure?

Non-causal explanations

Evidence of selection bias?

Evidence of information bias?

Evidence of confounding?

Evidence of chance?

Causal explanations

Is there a logical temporal relationship between the outcome and exposure?

Strength of association?

Dose-response relationship?

Consistency?

Does the exposure produce a specific outcome?

External validity

Can the results be applied to the eligible population?

Can the results be applied to the source population?

Can the results be applied to other populations?

Comparison with other evidence

Are the results biologically plausible?

Are the results consistent with other evidence?

Miscellaneous

Study size and power calculations?

Are the statistical analyses appropriate?

Are the results presented appropriately?

Are the conclusions drawn from the statistical analyses appropriate?

Are the references to other work justified?

Is all work by other scientists that is referred to adequately acknowledged?

Has the author omitted any reference to any significant work in the same field?

Additional comments

Statistical analyses were undertaken using Minitab version 14 statistical software and P values less than 0.05 were considered to be significant.

Results of statistical evaluation

Table 5 shows the incidence of heart disease and the frequency of survival found for diabetic cases and non-diabetic control cats. The proportion of diabetic cats with heart disease in the case-control study was five of 19 (26.3 per cent) compared with the lower rate of two of 57 (3.5 per cent) for controls. Similarly, the mortality rate amongst diabetic cats was 13 of 19 (68.4 per cent), which was much higher than that for controls at 23 of 57 (40.4 per cent). As to be expected, there was little difference in the proportions of cats of different sex and breeds between diabetic and non-diabetic cats in view of the controls being selected to match cases. The mean ages of cases and controls were 11.6 and 11.4 years respectively.

Results of the binary logistic regression analysis for an association between heart disease and the risk factors, age, sex, breed and diabetes are shown in Table 6. Diabetes was identified as a significant risk factor ($P=0.01$) with cats suffering from diabetes being 10.4 times more likely to have heart disease (95 per cent CI from 1.8 to 61.2). There was no association of heart disease with sex or breed and age did not have any significant effect on the risk of heart disease.

Table 7 similarly shows that the only significant risk factor ($P=0.002$) associated with mortality was diabetes. Cats with diabetes were 3.4 times more likely to die (95 per cent CI 1.1 to 10.6).

Examination of the distribution of the survival times of cats following recruitment to the study indicated that for controls, 50 per cent did not survive more than 718 days, whereas for diabetics, 50 per cent did not survive more than 385 days. The box plot of the survival times by diabetic category are shown in Fig 1. Multivariate regression analysis of the survival times indicated that sex and breed did not influence the survival times, whereas age and diabetes did, as shown in Table 8. Diabetic cats had significantly lower survival times ($P=0.002$) than controls and as age increased, the survival time of cats decreased significantly ($P=0.004$).

Table 5. Number of diabetic cats (cases) and non-diabetic cats (controls) in the case-control analyses classified according to the categorical variables investigated in the study

Variable	Level	Diabetic	
		Cases	Controls
Heart disease	No	14	55
	Yes	5	2
Survival	No	13	23
	Yes	6	34
Sex	Female neuter	7	21
	Male neuter	12	36
Breed	Domestic longhair	4	13
	Domestic shorthair	15	44

Table 6. Results from the multivariate binary logistic regression analysis showing the odds ratios, 95 per cent CI and significance (LRT P values) associated with the risk of heart disease for each of the categorical variables sex, breed and diabetes after adjustment for age of cat

Predictor	Odds ratio	Lower 95 per cent CI	Upper 95 per cent CI	LRT P value
Age (years)	0.92	0.69	1.24	0.50
Sex (referent group FN)				
MN	1.93	0.28	13.22	0.60
Breed (referent group DLH)				
DSH	1.93	0.28	13.22	0.57
Diabetes (referent group NO)				
YES	10.38	1.76	61.18	0.01

CI Confidence interval, LRT Likelihood ratio test, FN Female neutered, MN Male neutered, DLH Domestic longhair, DSH Domestic shorthair

Table 7. Results from the multivariate binary logistic regression analysis showing the odds ratios, 95 per cent CI and significance (LRT P values) associated with the risk of death for each of the categorical variables sex, breed and diabetes after adjustment for age of cat

Predictor	Odds ratio	Lower 95 per cent CI	Upper 95 per cent CI	LRT P value
Age (years)	1.15	0.95	1.38	0.15
Sex (referent group FN)				
MN	0.66	0.22	1.95	0.45
Breed (referent group DLH)				
DSH	0.53	0.14	1.98	0.35
Diabetes (referent group NO)				
YES	3.39	1.08	10.60	0.036

CI Confidence interval, LRT Likelihood ratio test, FN Female neutered, MN Male neutered, DLH Domestic longhair, DSH Domestic shorthair

DISCUSSION

The epidemiological features of diabetes mellitus in this group of cats from first-opinion practice are in keeping with those reported elsewhere with a notable predominance of males (Panciera and others 1990, Peterson 1998, Rand and Marshall 2004, Rand and others 2004). None of the cats were Burmese.

The present study is flawed because it addresses a small sample of diabetic cats seen at a single centre. It is also a retrospec-

tive study and retrospective studies should always be interpreted with caution.

A matched case-control design was chosen for this study in order to derive the maximum amount of meaningful information from a small number of diabetic cats. Three controls were chosen from the same practice as the cases; they were matched for age, breed and sex to each index case of diabetes. Each control case was enrolled into the study having been seen for a routine vaccination or a new episode of disease within a short time period

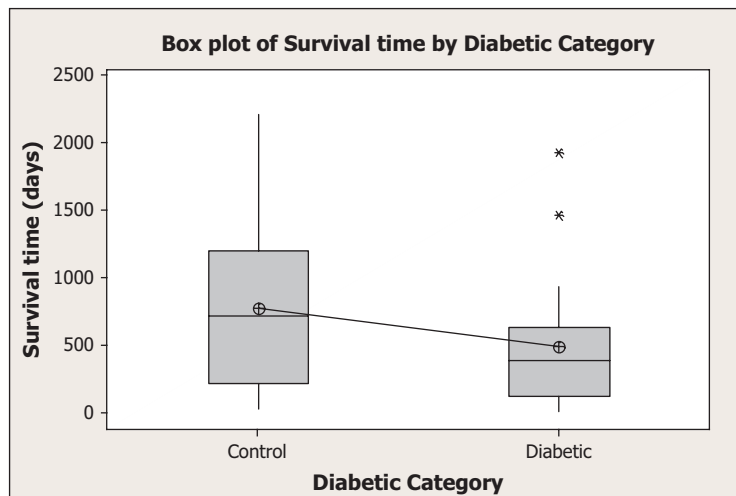


FIG 1. Box plot illustrating the difference in distribution of the survival times in days since recruitment to the study of control and diabetic cats. * represents outliers

before or after the index case. This design was chosen to attempt to select controls that did not differ systematically from the cases except for the absence of diabetes and to avoid over-representation of animals with other chronic disease processes in the control population.

The most important finding from this study is that heart failure was frequent in this sample of cats with diabetes mellitus. Moreover, all cats with heart failure died or were euthanased soon after the development of this condition. The findings from the case-control analyses have clearly identified diabetes as the one significant risk factor associated with both heart disease and mortality in this primary first-opinion practice. Age, breed and sex of the cat were not identified as risk factors. Diabetic cats were 10.4 times (95 per cent CI 1.8 to 61.2) more likely to have heart disease

and 3.4 times (95 per cent CI 1.1 to 10.6) more likely to die than their age-matched and breed-matched controls. These results are consistent with diabetic cats being more predisposed to heart disease, which in turn increases the risk of mortality. The survival time of diabetic cats from point of diagnosis did differ significantly from their controls and depended on the age of the cat. The median survival time of diabetic cats was just over one year (385 days) compared with almost two years (718 days) for their controls.

Of the six diabetic cats in this study identified as having heart failure, five of the six had a pleural effusion and two of the six had ascites, a finding, which is relatively uncommon in cats with heart failure. Three of these diabetic cats were found to have very enlarged left atria on

echocardiography; in the other two cases where echocardiography was permitted, the findings were also compatible with heart failure. In addition, three of these cats had serious dysrhythmias documented by electrocardiography (ECG; atrial fibrillation, ventricular premature complexes and third degree heart block). A fourth cat (case 7) also had a dysrhythmia audible on auscultation in the latter stages of the illness, ECG evaluation of the rhythm was not sanctioned by the owner so the exact nature of this rhythm disturbance remains obscure. One other cat (case 10) exhibited sinus bradycardia.

In the past, particularly before the advent of echocardiography, many cats with heart failure were probably misdiagnosed, because the most frequent signs of heart failure recognised in other veterinary species, such as coughing and tachycardias, are infrequently found in cats with heart failure. If a cat has a pleural effusion, cardiac auscultation is often very challenging so that heart murmurs or gallop sounds may not be identified with ease. Moreover, until fairly recently, cats with pleural effusions were often designated as having idiopathic effusions or other thoracic disease without performing echocardiographic studies. These observations may explain why heart failure has not been identified as a frequent complication of diabetes mellitus in cats.

The forms of heart disease and failure, which the cats in this study exhibited, were by no means identical; some showed signs compatible with hypertrophic cardiomyopathy, whereas others showed signs principally indicating right-sided heart failure. This heterogeneity in clinical appearance suggests that diabetes mellitus probably does not cause cardiac disease in cats directly or simply. However, in this species, as in the human sufferer, diabetes mellitus may promote or exacerbate existing heart disease. It is unfortunate that systemic blood pressures were not measured in these diabetic cats because if hypertension were present it might offer one explanation for the development of heart failure. Many human diabetics are hypertensive. On the contrary, limited data suggest that hypertension is not common in feline diabetics (Sennello and others 2003).

Table 8. Results from the multivariate survival time (days) analysis showing the regression coefficients, 95 per cent CIs and significance (P values) associated with each of the categorical variables sex, breed and diabetes after adjustment for age of cat and fitting a Weibull distribution taking account of right censoring

Predictor	Coefficient	Lower 95 per cent CI	Upper 95 per cent CI	P value
Shape	1.0219	0.7787	1.3411	–
Age (years)	–0.1877	–0.3168	–0.0586	0.004
Sex (referent group FN)				
MN	–0.1139	–0.8749	0.6472	0.769
Breed (referent group DLH)				
DSH	0.4162	–0.4429	1.2754	0.342
Diabetes (referent group NO)				
YES	–1.1052	–1.7899	–0.4206	0.002

CI Confidence interval, FN Female neutered, MN Male neutered, DLH Domestic longhair, DSH Domestic shorthair

It is possible that one or more of these diabetic cats with heart failure might have had acromegaly, a disease which is known to cause diabetes and heart failure in cats (Peterson and others 1990). However, the usual principal sign of acromegaly is uncontrolled hyperglycaemia in spite of insulin dosage exceeding 20 iu per day (Norman and Mooney 2000, Peterson 2004). The maximum dose of insulin given to a cat in this study was 12 iu per day. Acromegaly is also much less common than uncomplicated diabetes mellitus. However, in none of the cats in the present study was insulin-like growth factor measured and no other tests were used to deliberately seek out cases of acromegaly.

One or more of the cats with diabetes and heart failure could have had hyperthyroidism, a disease which is very common in older cats and which sometimes can cause heart failure (Mooney and Petersen 2004). Diabetic cats with known hyperthyroidism were deliberately excluded from this study in the recruitment criteria. Signs of thyroid enlargement were regularly sought by clinical examination of the diabetic cats and thyroid assays were performed in 10 cats during the course of their illness, including three of those cats found to develop heart failure. None of these cats was diagnosed as suffering from hyperthyroidism but, because routine thyroid monitoring was not performed in all cases, this possibility cannot be excluded.

Studies of the prognosis and outcome for cats with diabetes have been relatively few. However, if we examine some of these publications, most of which describe cases from secondary or tertiary referral hospitals, we discover that in common with the observations in the present study, heart disease may have been present in a considerable number of these diabetic cats. For instance, in a large study of 104 cats with diabetes (Crenshaw and Peterson 1996), concurrency between diabetes mellitus and heart disease was not remarked upon as an important finding and yet heart murmurs (19 of 104) and gallop rhythms (seven of 104) were frequently identified during physical examination of these cats. Additionally, these authors reported cardiac enlargement in

14 of 52 cases (27 per cent) where a chest radiograph was taken. In another much smaller study, which investigated the effects of diet on glycaemia in 16 diabetic cats (Nelson and others 2000), at the time of entry into the study two cats had heart murmurs and another two cats exhibited audible cardiac gallop sounds. A recent publication, which focused on cats in an emergency hospital, also reported heart murmurs and gallop sounds in a significant proportion of cats with diabetes seen in crisis situations (Koenig and others 2004). Congestive heart failure was recorded in five of 17 cats with hyperglycaemic hyperosmolar syndrome, one of 33 cats with diabetic ketoacidosis and six of 78 cats with uncomplicated diabetes mellitus. Again the authors did not recognise or report an overt relationship between diabetes mellitus and heart failure. However, in two other retrospective studies of diabetes mellitus, heart disease or heart failure were not reported at all in diabetic cats (Kraus and others 1997, Goossens and others 1998).

In human beings, diabetes mellitus is an independent risk factor for the development of heart disease and heart failure. The exact relationship between diabetes and cardiovascular disease in people is complex. Diabetes causes an atherogenic dyslipidaemia, which leads to accelerated coronary artery disease and myocardial ischaemia. A specific myocardial disease, diabetic cardiomyopathy, is also reported. Hypertension, an autonomic neuropathy leading to decreased cardiac vagal tone, glycation of myocardial proteins and endothelial dysfunction may all contribute to the development of diabetic cardiomyopathy, but human diabetics are also frequently obese and chronically physically inactive and this lifestyle appears to contribute to both diabetes and heart disease (Julu 1993, Grundy and others 1999, McNally and Lawrence 2003, Almdal and others 2004, Bell 2004, Bertoni and others 2004, Nichols and others 2004). Cardiovascular diseases are listed as the cause of death in about 65 per cent of persons with diabetes (Grundy and others 1999).

Diet and exercise probably are important in the aetiology of diabetes in cats, as they are in people (Rand and Marshall

2005). Eighty years ago, Joslin drew attention to a link between diabetes, obesity and cardiovascular disease in people (Joslin 1927). A similar link may exist in the cat. The implications of these findings for both veterinary and comparative medicine certainly warrant further investigation.

Acknowledgements

We would like to thank the nursing and veterinary staff at Barton Veterinary Hospital for their dedication in the care of these patients. We also thank the secretarial and reception staff at Barton Veterinary Hospital, particularly Angela Francis, who tirelessly interrogated our computer records for this study.

The active support and encouragement of CVS (UK) Ltd, owners of The Barton Veterinary Hospital, is gratefully acknowledged.

CL did much of this work whilst in receipt of a Blue Skies Research Grant from the RCVS Trust.

References

- ALMDAL, T., SCHARLING, H., JENSEN, J. S. & VESTERGAARD, H. (2004) The independent effect of type 2 diabetes mellitus on ischaemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Archives of Internal Medicine* **164**, 1422-1426
- BELL, D. S. H. (2004) Heart failure: a serious and common comorbidity of diabetes. *Clinical Diabetes* **22**, 61-65
- BERTONI, A. G., HUNDLEY, W. G., MASSING, M. W., BONDS, D. E. & BURKE, G. L. (2004) Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* **27**, 699-703
- CRENSHAW, K. L. & PETERSON, M. E. (1996) Pretreatment clinical and laboratory evaluation of cats with diabetes mellitus: 104 cases (1992-1994). *Journal of the American Veterinary Medical Association* **209**, 943-948
- GOOSSENS, M. M. C., NELSON, R. W., FELDMAN, E. C. & GRIFFEY, S. M. (1998) Response to insulin treatment and survival in 104 cats with diabetes mellitus (1985-1995). *Journal of Veterinary Internal Medicine* **12**, 1-6
- GRUNDY, S. M., BENJAMIN, I. J., BURKE, G. L., CHAIT, A., ECKEL, R. H., HOWARD, B. V., MITCH, W., SMITH, S. C. J. & SOWERS, J. R. (1999) Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* **100**, 1134-1146
- JACOBS, G. & KNIGHT, D. H. (1985) M-mode echocardiographic measurements in non-anaesthetised healthy cats: effects of body weight, heart rate, and other variables. *American Journal of Veterinary Research* **46**, 1705-1711
- JOSLIN, E. P. (1927) Arteriosclerosis in diabetes. *Annals of Clinical Medicine* **5**, 1061-1079
- JULU, P. O. O. (1993) Vagolytic effect of diabetes mellitus. *Brain* **116**, 485-492
- KOENIG, A., DROBATZ, K. J., BEALE, A. B. & KING, L. G. (2004) Hyperglycaemic, hyperosmolar syndrome in feline diabetics: 17 cases (1995-2001). *Journal of Veterinary Emergency and Critical Care* **14**, 30-40

- KRAUS, M. S., CALVERT, C. A., JACOBS, G. J. & BROWN, J. (1997) Feline diabetes mellitus: a retrospective mortality study of 55 cats (1982-1994). *Journal of the American Animal Hospital Association* **33**, 107-111
- LISTER, A. L. & BUCHANAN, J. W. (2000) Measurement of the normal feline cardiac silhouette on thoracic radiographs. *Journal of the American Veterinary Medical Association* **216**, 210
- MCNALLY, P. G. & LAWRENCE, I. G. (2003) Diabetic autonomic neuropathy and the cardiovascular system. In: *Heart Disease and Diabetes*. Ed M. Fisher. Martin Dunitz, London and New York. pp 35-64
- MOONEY, C. T. & PETERSEN, M. E. (2004) Feline hyperthyroidism. In: *BSAVA Manual of Small Animal Endocrinology*. 3rd edn. Eds C. T. Mooney and M. E. Peterson. British Small Animal Veterinary Association, Gloucester, UK. pp 95-111
- NELSON, R. W., SCOTT-MONCRIEFF, J. C., FELDMAN, E. C., DEVRIES-CONCANNON, S. E., KASS, P. H., DAVENPORT, D. J., KIERNAN, C. T. & NEAL, L. A. (2000) Effect of dietary insoluble fiber on control of glycaemia in cats with naturally acquired diabetes mellitus. *Journal of the American Veterinary Medical Association* **216**, 1082-1088
- NICHOLS, G. A., GULLION, C. M., KORO, C. E., EPHROSS, S. A. & BROWN, J. B. (2004) The incidence of congestive heart failure in type 2 diabetes. *Diabetes Care* **27**, 1879-1884
- NORMAN, E. J. & MOONEY, C. T. (2000) Diagnosis and management of diabetes mellitus in five cats with somatotrophic abnormalities. *Journal of Feline Medicine and Surgery* **2**, 183-190
- PANCIERA, D. L., THOMAS, C. B., EICKER, S. W. & ATKINS, C. E. (1990) Epizootiologic patterns of diabetes mellitus in cats: 333 cases (1980-1986). *Journal of the American Veterinary Medical Association* **197**, 1504-1508
- PETERSON, M. E. (1998) Feline diabetes mellitus. In: *BSAVA Manual of Small Animal Endocrinology*. 2nd edn. Eds A. G. Torrance and C. T. Mooney. British Small Animal Veterinary Association, Gloucester, UK. pp 97-102
- PETERSON, M. E. (2004) Acromegaly. In: *BSAVA Manual of Small Animal Endocrinology*. 3rd edn. Eds C. T. Mooney and M. E. Peterson. British Small Animal Veterinary Association, Gloucester, UK. pp 187-192
- PETERSON, M. E., TAYLOR, R. S., GRECO, D. S., NELSON, R. W., RANDOLPH J. F., FOODMAN, M. S., MOROFF, S. D., MORRISON, S. A. & LOTHROP, C. D. (1990) Acromegaly in 14 cats. *Journal of Veterinary Internal Medicine* **4**, 192-201
- PIPERS, F. S., REEF, V. & HAMLIN, R. L. (1979) Echocardiography in the domestic cat. *American Journal of Veterinary Research* **40**, 882-886
- RAND, J. S. & MARSHALL, R. (2004) Feline diabetes mellitus. In: *BSAVA Manual of Canine and Feline Endocrinology*. 3rd edn. Eds C. T. Mooney and M. E. Peterson. British Small Animal Veterinary Association, Gloucester, UK. pp 129-141
- RAND, J. S. & MARSHALL, R. (2005) Understanding feline diabetes mellitus: pathogenesis and management. *Waltham Focus* **15**, 5-11
- RAND, J. S., FLEEMAN, L. M., FARROW, H. A., APPLETON D. J. & LEDERER, R. (2004) Canine and feline diabetes mellitus: nature or nurture? *The Journal of Nutrition* **134**, 2072S-2080S
- SENNELLO K. A., SCHULMAN R. L., PROSEK R. & SIEGEL A. M. (2003) Systolic blood pressure in cats with diabetes mellitus. *Journal of the American Veterinary Medical Association* **223**, 198-201
- SISSON, D. D., KNIGHT, D. H., HELSINKI, C., FOX, P. R., BOND, B. R., HARPSTER, N. K., MOISE, N. S., KAPLAN, P. M., BONAGURA, J. D., CZAMECKI, G. & SCHAEFFER, D. J. (1991) Plasma taurine concentrations and M-mode echocardiographic measures in healthy cats and cats with dilated cardiomyopathy. *Journal of Veterinary Internal Medicine* **5**, 232-238