Factors associated with clinical remission in cats with diabetes mellitus

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Abstract

Type 2 diabetes mellitus is a common endocrine disease in cats. The aim of this study was to investigate factors that are associated with clinical remission in diabetic cats, and those that might influence survival time. Medical records of 29 cats with diabetes mellitus were evaluated retrospectively. Data collected from each record included breed, age, and sex, types of diet before and after admission, degree of weight loss, duration of clinical signs before admission, elevation of alanine aminotransferase activity and ketonuria at the time of admission, concurrent pancreatitis or renal failure, glipizide administration, insulin supplement, and survival time. The diet after establishing diagnosis (restriction to non-carbohydrate canned food) was the only factor that was significantly associated with achieving clinical remission ($P < 0.001$). Survival time of cats was positively associated ($P = 0.004$) with clinical remission status and the type of diet after admission ($P = 0.04$) and negatively associated with the presence of chronic renal failure ($P = 0.04$). This was the first report of feline diabetes mellitus from Taiwan.

Carbohydrate, dietary management, renal failure, diabetic cats, survival

Diabetes mellitus (DM) is a common endocrine disease in cats. This condition is characterized by hyperglycaemia, which results from an absolute or relative deficiency of insulin. Feline type 2 DM is associated with inadequate insulin secretion and concurrent conditions that induce insulin resistance or diabetogenic drugs that are associated with the development of DM (Zini et al. 2010). Clinical remission of this condition can be achieved by improving the residual β-cell function and restoring euglycaemia, for example, good glycaemic control during the early stage of the disease (Roomp and Rand 2009).

Researchers have investigated the predictors of clinical remission in cats with diabetes mellitus, including age, serum cholesterol concentrations, strict glycaemic control, and the method of insulin replacement (Marshall et al. 2009; Zini et al. 2010). However, predictors of survival in cats with diabetes mellitus were not fully explored.

The aim of this study was to investigate factors that are associated with clinical remission in cats with diabetes mellitus, and those that might influence the survival time.

Materials and Methods

Case selection

The medical records of cats in which DM was diagnosed at the Azu Clinic for Animals, Taipei city, Taiwan, between 1999 and 2011 were reviewed retrospectively. The inclusion criteria for cats with DM in this survey were the presence of persistent hyperglycaemia (>16.7 mmol/l) and presence of glycosuria in at least 2 separate urine samples for a period longer than 2 weeks, and the presence of clinical signs consistent with DM. Criteria for the achievement of clinical remission was normoglycaemia (< 8.3 mmol/l) that was maintained without insulin for at least 4 weeks.

Twenty-nine cats fulfilled the inclusion criteria, there were 18 domestic short-hairs (DSH), 10 Persians, and 1 domestic long-hair (DLH) cat. There were 19 castrated males (MC), 4 intact males (MI), 4 spayed females (FS), and 2 intact females (FI). The mean age was 8.0 ± 3.5 years, and the mean body weight was 4.6 ± 1.5 kg. Among these 29 cats, 16 (55%) achieved clinical remission. The group that achieved clinical remission included 11 DSHs and 5 Persians (11 MC, 3 MI and 2 FS cats). The mean age was 7.5 ± 4.2 years (range 2–16 years). The mean body weight was 4.2 ± 1.3 kg (range 2.8–7.7 kg). The mean time to achieve clinical remission was

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45.5 ± 60 days. The group of cats that remained insulin-dependent included 7 DSHs, 5 Persians and 1 DLH (8 MC, 1 MI, 2 FS and 2 FI). The mean age was 8.7 ± 2.3 years (range 6–13 years). The mean body weight was 4.9 ± 1.6 kg (range 2.8 to 7.4 kg).

Statistical analysis

The factors (non-numeric data, such as breed, sex, type of diet before admission, type of diet after admission, presence of ketonuria, concomitant elevation of ALT activity, presence of concurrent pancreatitis or chronic renal failure at the time of admission, application of glucose lowering agents and insulin supplementation) that may be associated with remission status were evaluated with Pearson's chi-square. Numeric data (age, body weight, degree of weight loss, duration of pre-admission clinical signs of DM, and survival time) were analyzed using one-way analysis of variance (normally distributed data), and the Kruskal-Wallis test (non-normally distributed data). A Kaplan-Meier survival curve was plotted. Cats that were alive at the conclusion of the study were censored. Variables that might have influenced survival time, including sex, age at diagnosis, body weight, degree of weight loss, the duration of pre-admission clinical signs of DM present before admission, diet before and after admission, ALT activity, remission status, and concurrent pancreatitis or renal failure at the time of admission were analyzed with a Cox proportional hazard model. All statistical analyses were performed with SPSS software (Statistical Package for the Social Sciences, version 13.0; SSPS Inc., Illinois, USA). Continuous data are presented as means ± standard deviation. ignificance was set at $P \leq 0.05$.

Results

Factors before diagnosis

The degree of weight loss before admission in cats that achieved clinical remission and those that remained insulin-dependent was 16% ± 8% (range 7–30%), and 22% ± 13% (range 0–48%), respectively. The duration of pre-admission clinical signs associated with DM in the cats that achieved clinical remission was 44.7 ± 35.6 days (range 2–120 days), compared to 37.6 ± 27.9 days (range 10–112 days) in the cats that remained insulin-dependent. There were no significant differences with regards to breed ($P = 0.45$), sex ($P = 0.36$), age ($P = 0.36$), body weight ($P = 0.22$) or degree of weight loss ($P = 0.17$) and the duration of pre-admission clinical signs ($P = 0.56$) between these two groups.

Before diagnosis, 14 cats were on dry food exclusively, 2 were fed mixed dry and canned food in cats that achieved clinical remission. In the cats that remained insulin-dependent, 11 were on dry food exclusively, while 2 were fed mixed dry and canned food. No significant difference between these two groups was found ($P = 0.62$).

Concurrent disorders

The presence of ketonuria, elevated alanine aminotransferase (ALT) activity, concurrent pancreatitis and chronic renal failure in the cats that achieved clinical remission compared to those that remained insulin-dependent was 31% (5/16) versus 33% (3/10), 44% (7/16) versus 31% (4/13), 19% (3/16) versus 31% (4/13), and 0% (0/16) versus 15% (2/13), respectively. Neither the presence of pre-existing conditions (ketonuria, $P = 0.47$; elevation of ALT, $P = 0.43$) or concurrent medical disorders (pancreatitis, $P = 0.46$; chronic renal failure, $P = 0.19$) was significantly different between these two groups.

Factors after diagnosis

After the diagnosis of DM was made, glipizide (0.25 mg/kg orally, q 12 h; China Chemical & Pharmaceutical Co. Ltd., Taipei, Taiwan) was administered to 44% (7/16) cats that achieved clinical remission and to 54% (7/13) cats that remained insulin-dependent. Insulin (0.1–0.9 U/kg, q 12–24 h; Caninsulin®, Intervet/Schering-Plough Animal Health/Merck Animal Health, the Netherlands) was given to 75% (12/16) cats that achieved clinical remission and to 92% (12/13) cats that remained insulin-dependent. Neither the use of glipizide ($P = 0.43$) nor insulin supplementation ($P = 0.24$) was associated with clinical remission. In this study Caninsulin® was given at 0.2 U/kg, twice daily on the day one of admission. Blood glucose levels were measured every 2 h for 12 h, starting immediately before the morning insulin injection. Caninsulin® dosage was increased, reduced or left unchanged when the nadir was > 11 mmol/l, < 5 mmol/l, or within 5 to 11 mmol/l. Resolution or marked improvement in clinical signs, and increased body weight was considered as good glycaemic control.

After the diagnosis of DM, all cats were fed whatever the cats preferred. The daily caloric intake ranged from 60 to 80 kcal/kg/day based on individual body weight and degree of weight loss. In the group that achieved clinical remission, 15 cats were fed canned food exclusively, and 1 was fed mixed dry and canned food. In the cats that remained insulin-dependent, 3 were on canned food exclusively, and 10 were fed mixed dry and canned food. There was a significant difference in the rate of remission between cats fed different food types after diagnosis ($P < 0.001$).

Among the 16 cats that achieved clinical remission, age, body weight, and degree of weight loss were not associated with the time to achieve clinical remission. Univariate analysis indicated that increased time to reach clinical remission was associated with a prolonged duration of clinical signs before admission ($P = 0.02$, $r = 0.57$).

Gross nutrient composition of the diets

The types of dry food before admission included various regular, maintenance, or prescription diets for adult cats. The types and particular formulations of the dry food were not assessed as most cats were fed various or mixed dry foods prior to admission. Based on information provided by the pet food manufacturers, the gross nutrient composition of the dry foods used in this study had the following ranges: 23%–51.1% protein, 10%–21.8% fat, 10%–43.5% carbohydrates, 0.3%–14.3% fibre and 5.5%–10% water/moisture. Based on information provided by the pet food manufacturers, the types of canned food used in this study were mainly made of tuna fish or chicken, and the gross nutrient composition of the canned foods used in this study had the following ranges: 12%–13% protein, 0.2%–1% fat, 0.1%–1% fibre and 83%–88% water/moisture.

Outcomes

Of the 29 treated cats, 15 were alive at the end of the study (11/16 in the clinical remission group and 4/13 in the insulin-dependent group). The mean survival times in the clinical remission and insulin-dependent groups were 36.8 ± 41.3 months and 11.8 ± 7.8 months, respectively (Fig 1, $P = 0.041$). The results of the Cox proportional hazard model indicated

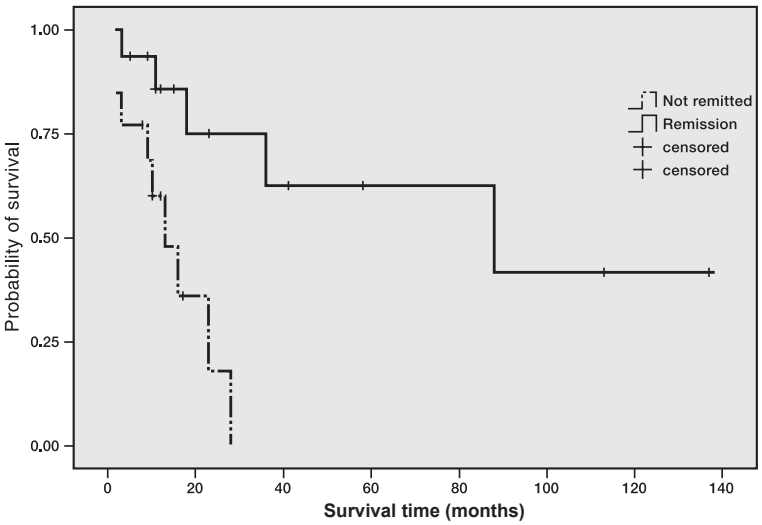

Fig. 1. Kaplan-Meier survival curve indicating the probability of survival after the diagnosis of diabetes mellitus in 29 cats. Data for cats living (n = 15) at the conclusion of the study were not included. Hatch marks indicate censored cats.

that survival time was positively associated with clinical remission status ($P = 0.004$) and type of diet after diagnosis ($P = 0.047$). Survival time was negatively associated with the presence of chronic renal failure ($P = 0.040$), but not affected by sex, age, body weight, degree of weight loss, type of diet before admission, duration of clinical signs before admission, elevation of ALT activity, presence of ketonuria, concurrent pancreatitis at the time of diagnosis, glipizide or insulin supplementation. None of the cats that achieved clinical remission experienced recurrence of DM.

Discussion

The clinical remission rate of DM in the cats in this study was 55%. This rate was expected to be higher as cats with a medical history of glucocorticoid treatment were not excluded from our study. Glucocorticoids are known to have diabetogenic effects in cats (Lien et al. 2006).

Based on the results of our study, diet after admission was the only factor that was significantly associated with the achievement of clinical remission. Diabetic cats were significantly more likely to reach clinical remission when fed non-carbohydrate-based canned food. As carnivores, cats lack salivary amylase and have low levels of pancreatic amylase activity, which indicates that the dietary requirement of carbohydrates is low in cats (Kienzle 1993a,b). Compared to moderate-carbohydrate diets, low-carbohydrate diets are more likely to have well-regulated glucose responses and achieve clinical remission in diabetic cats (Mazzaferro et al. 2003; Bennett et al. 2006). Low-carbohydrate diets may reduce postprandial insulin secretion and substantially preserve the residual function of β-cells in the pancreas (Mazzaferro et al. 2003). Diabetic cats in our study exhibited significantly higher rates of clinical remission when fed non-carbohydrate canned food. The results of this study reflect the nature of nutritional requirements in cats. Further studies are needed to clarify the effect of non-carbohydrate diet on prevention of diet-induced DM in cats.

The application of insulin and glucose-lowering agents together with a low-carbohydrate diet has been reported to improve glycaemic control. The longer a cat has unregulated DM, the less likely remission becomes (Mazzaferro et al. 2003; Marshall et al. 2009; Roomp and Rand 2009). In our study, glipizide administration and insulin therapy were not associated with clinical remission. Higher percentage of insulin-dependent cats had been administered glipizide and Caninsulin® compared to the cats that achieved clinical remission. All these cases were not newly diagnosed. Prolonged hyperglycaemia may cause irreversible damage to the pancreatic β-cells with a permanent loss in function. Either glipizide or Caninsulin® alone could not restore the function of residual β-cells after prolonged hyperglycaemia without administration of glucose-lowering agents at an early stage of DM. Nonetheless, as expected, there was an association between the increased time required to achieve clinical remission and the increased duration of clinical signs before diagnosis.

Concurrent disorders that may affect glycaemic control are generally believed to affect the chance of clinical remission, and can even affect survival time. However, the results reported in previous studies are inconsistent (Goossens et al. 1998; Nelson et al. 1999; Zini et al. 2010). Although ALT activities were elevated, ketonuria and pancreatitis were not associated with survival time or remission in our study, and concurrent chronic renal failure was negatively associated with survival time. The mean survival time between cats that reached clinical remission and those that remained insulin-dependent was significantly different. Survival time was significantly associated with the type of diet after diagnosis and the achievement of remission. These findings have not been previously reported in the veterinary literature.

In conclusion, diet (restricted to non-carbohydrate canned food) after diagnosis of DM in cats was significantly associated with the achievement of clinical remission and the survival time.

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