



Prednisolone-induced diabetes mellitus in the cat: a historical cohort

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Abstract

Objectives Prednisolone is a commonly used drug in cats and potential adverse effects include hyperglycaemia and diabetes mellitus. The aims of this study were to evaluate the frequency and investigate potential predisposing risk factors for the development of prednisolone-induced diabetes mellitus (PIDM) in cats.

Methods The electronic records of a tertiary referral centre were searched for cats receiving prednisolone at a starting dose of ≥ 1.9 mg/kg/day, for >3 weeks and with follow-up data available for >3 months between January 2007 and July 2019. One hundred and forty-three cats were included in the study.

Results Of the 143 cats, 14 cats (9.7%) were diagnosed with PIDM. Twelve out of 14 cats (85.7%) developed diabetes within 3 months of the initiation of therapy.

Conclusions and relevance Cats requiring high-dose prednisolone therapy should be closely monitored over the first 3 months of therapy for the development of PIDM.

Keywords: Glucocorticoid-induced hyperglycaemia; corticosteroid; hyperglycaemia; glucosuria

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Introduction

Diabetes mellitus (DM) is one of the most commonly diagnosed endocrine diseases in cats. DM is characterised by clinical signs including polyuria and polydipsia due to persistent hyperglycaemia and glucosuria as well as polyphagia and weight loss owing to an absolute or relative lack of insulin.¹ Most cats develop a disease comparable to type 2 DM in people and it is thought to develop due to a combination of insulin resistance and beta-cell dysfunction owing to environmental and genetic factors.² Environmental factors include obesity³ and glucocorticoid administration.⁴ Glucocorticoids are commonly used drugs in veterinary medicine for the treatment of a variety disorders due to their anti-inflammatory and immune-suppressive properties.⁵ Although they are widely used, they also cause a range of adverse effects, including alterations on glucose homeostasis. Glucocorticoid-induced diabetes mellitus (GIDM) is well recognised in humans.⁶ Dose and duration of therapy as well as patient body weight, among others, have been described as risk factors for the development of GIDM.

In feline patients, glucocorticoids have been suggested as a predisposing factor for the development of

DM⁴ and experimental studies have shown the diabetogenic effects of prednisolone, dexamethasone, methylprednisolone and fluorohydrocortisone in cats.^{7–10} Despite prednisolone being perhaps the most commonly used glucocorticoid in cats, prednisolone-induced diabetes mellitus (PIDM) is a poorly described entity in clinical practice. The aim of this study was to determine the prevalence of PIDM in a feline referral population receiving prednisolone therapy and to further characterise potential predisposing factors in the development of PIDM.

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Materials and methods

Selection of cases

The study protocol was approved by the Ethics Committee of the Royal Veterinary College (Royal Veterinary College Ethical Approval Number URN2017 – 1513). The electronic medical record system of a tertiary referral institution was searched from January 2007 to July 2019 using the following search terms: cat, feline, prednisolone, pred, steroids, corticosteroids and glucocorticoids. Identified records were then reviewed in detail and referring veterinarians were contacted by telephone or email to obtain follow-up information where necessary. Cats were included for analysis if the following criteria were all met: (1) initial prednisolone dose was ≥ 1.9 mg/kg/day; (2) duration of treatment was a minimum of 3 weeks; and (3) follow-up data for at least 3 months after initiation of prednisolone therapy was available.

Cats that had received glucocorticoid therapy within 3 weeks of presentation or were diabetic prior to, or at the time of, presentation and cats with neoplastic diseases, including feline hyperadrenocorticism, were excluded.

Cats were considered to have developed PIDM if they had typical clinical signs associated with DM (eg, polyuria, polydipsia, weight loss and polyphagia) and if they had fulfilled one of the following criteria: (1) hyperglycaemia (>8.1 mmol/l on more than two occasions) in conjunction with glucosuria; and (2) hyperglycaemia in conjunction with increased fructosamine levels.

Medical records review

The following details were extracted from the medical records in all cats: signalment (age, sex, body weight and breed), working or final diagnosis and initial prednisolone dose, duration of prednisolone therapy, frequency of administration and development of PIDM. In addition, serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities, serum cholesterol concentration, urine specific gravity, glucosuria measured by urine colorimetric dipstick, blood glucose concentration and body condition score (BCS, scoring from 1 to 9 where 4 and 5 were considered normal) on presentation were noted when available.

Statistical analysis

Data were compiled in Microsoft Excel and imported into Stata 15 (Stata), which was used for all statistical analyses. A P value of <0.05 was considered statistically significant. The continuous variables were assessed graphically and by the Shapiro–Wilk’s test for normality and are presented as medians (ranges). The categorical variables are described as numbers (percentages). Breed was categorised as purebred or mixed breed for the statistical analysis. Associations between categorical and continuous variables were explored by the two-sample t -test and Wilcoxon rank sum test for normally and non-normally

distributed variables, respectively. Associations between categorical variables were tested using the χ^2 test or Fisher’s exact test. Univariable logistic regression was used to explore the relationship between prednisolone dose and PIDM development. Kaplan–Meier curves were used to visualise time to the development of diabetes in the PIDM group and cats were censored if they died or were lost to follow-up. Box plots were used to visualise prednisolone starting doses between the groups. Multivariable analysis was not performed due to the lack of statistical power and limited number of cases.

Results

Signalment and underlying causes

One hundred and forty-three cats fulfilled all of the inclusion criteria (see Figure 1). Of these, 66 (46%) were male and 77 (54%) were female. Breed distribution is shown in Table 1. Fourteen of 143 cats (9.8%) were diagnosed with PIDM. None of the cats developing PIDM were Burmese. The median overall age at the time of presentation was 5.9 years (0.6–18) and no significant difference in age was found in cats developing PIDM and cats that did not develop PIDM ($P = 0.895$).

Overall median body weight was 4.0 kg (2.4–7.9) and no significant difference in body weight between the PIDM group and non-PIDM group was identified ($P = 0.980$). BCS was recorded in 100/143 cases (13/14 of the PIDM group and 87/129 of the non-PIDM group), and the median BCS for both groups was 4/9. There were no statistical differences in breed, sex distribution

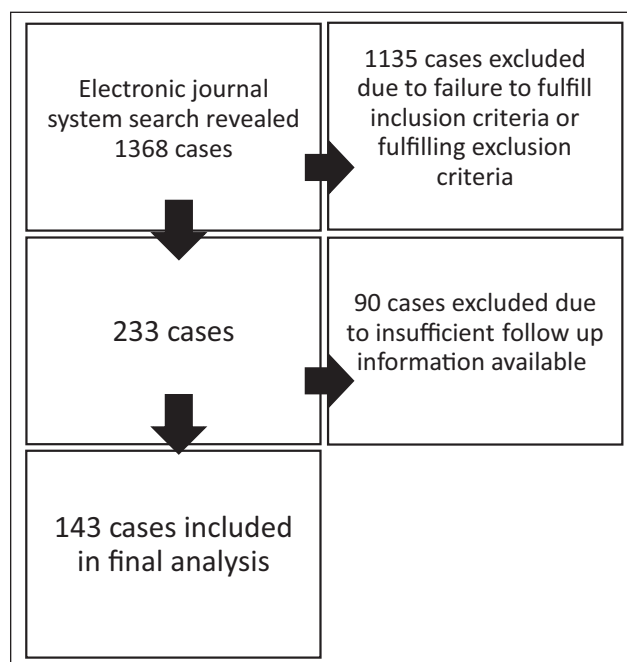


Figure 1 Inclusion details of 143 cats in a cohort study of prednisolone-induced diabetes mellitus

Table 1 Breed distribution of 143 cats in a cohort study of prednisolone-induced diabetes mellitus

Breed	n
Domestic shorthair	82
Domestic longhair	10
Persian	8
Bengal	6
Maine Coon	6
British Shorthair	5
Burmese	5
British Blue	4
Siamese	4
Mixed breed	2
Russian Blue	3
Oriental Shorthair	2
Burmilla	1
Chantilly–Tiffany	1
Devon Rex	1
Korat	1
Norwegian Forest Cat	1
Snowshoe	1

Table 2 Descriptive features of 143 cats in a cohort study of prednisolone-induced diabetes mellitus (PIDM)

Variables	PIDM	non-PIDM	Overall
Age (years)	7.5 (1.2–13.2)	5.9 (0.6–18.0)	5.9 (0.6–18.0)
Weight (kg)	4.5 (2.2–5.4)	4.0 (2.2–8.1)	4.0 (2.2–8.1)
BCS (1–9)	4 (2–7)	4 (1–9)	4 (1–9)
Sex			
Male entire	1 (7.1)	3 (2.3)	4 (2.8)
Male neutered	7 (50.0)	55 (42.6)	62 (43.4)
Female entire	0 (0.0)	2 (1.6)	2 (1.4)
Female neutered	6 (42.9)	69 (53.5)	75 (52.5)

Continuous variables reported as a median (range) and categorical variables as number (%)

BCS = body condition score

or neuter status between the two groups ($P = 0.238$, $P = 0.385$ and $P = 0.467$, respectively; see Table 2 for further details). Immune-mediated haemolytic anaemia, inflammatory bowel disease and dermatological diseases were the three most common underlying diseases treated with prednisolone (Table 3). Seven (50%) of the cats developing PIDM were treated for immune-mediated haemolytic anaemia, two cats were treated for IBD and two for dermatological diseases. One cat was treated for each of the following diseases: pure red cell aplasia, chronic rhinitis and cholangitis.

PIDM and hyperglycaemia

The median prednisolone starting dose for the study population as a whole was 3.0 mg/kg. The PIDM group received higher daily starting doses of prednisolone

Table 3 Details of underlying causes in 143 cats in a cohort study of prednisolone-induced diabetes mellitus

Diagnosis	n
Immune-mediated haemolytic anaemia	58
Inflammatory bowel disease	22
Dermatological diseases	21
Feline asthma	12
Immune-mediated thrombocytopenia	8
Inflammatory or immune-mediated disease suspected, but not confirmed	3
Hepatitis or cholangiohepatitis	3
Inflammatory ocular disease	3
Neurological diseases	1
Chronic rhinitis	1
Polyarthropathy	1
Myelodysplastic syndrome	1
Red cell aplasia	1
Idiopathic hypercalcemia	1
Laryngitis	1

than the non-PIDM group (median 3.5 [2.0–4.4] vs 2.9 [1.9–5.0] mg/kg/day, Figure 2), but this was not statistically significant ($P = 0.164$). The median length of prednisolone treatment was 6 months and no statistical difference was found in duration of prednisolone therapy ($P = 0.284$) between the groups. One of the 14 (7%) cats in the PIDM group was administered prednisolone twice daily, and 23/129 (17%) in the non-PIDM group. Nine of the 14 (65%) cats developing PIDM were started on insulin therapy.

Twelve of the 14 cats in the PIDM group received the diagnosis within the first 3 months of treatment (Figure 3). The remaining two cats were never tapered off their prednisolone therapy and both developed DM following a prednisolone dose increase (from 1.0 mg/kg to 1.7 mg/kg and from 0.25 mg/kg to 2 mg/kg, respectively) after being diagnosed with a relapse of their underlying immune-mediated disease (thrombocytopenia and anaemia) after 108 and 128 weeks being on prednisolone, respectively.

The assessed clinicopathological values, measured prior to prednisolone therapy, are summarised in Table 4. Neither blood glucose concentration, serum cholesterol concentration, serum ALP nor ALT activities were associated with the development of PIDM ($P = 0.180$, $P = 0.623$, $P = 0.418$ and $P = 0.513$, respectively). Urinalysis prior to prednisolone treatment was available in 9/14 cats of the PIDM group and 72/129 cats of the non-PIDM group. Glucosuria was detected in 4/9 (44.4%) and 11/72 (15.3%) of the cats, respectively ($P = 0.056$).

Discussion

The prevalence of PIDM was 9.7% in our study. This is lower than the reported prevalence of 18.7% in people,⁶

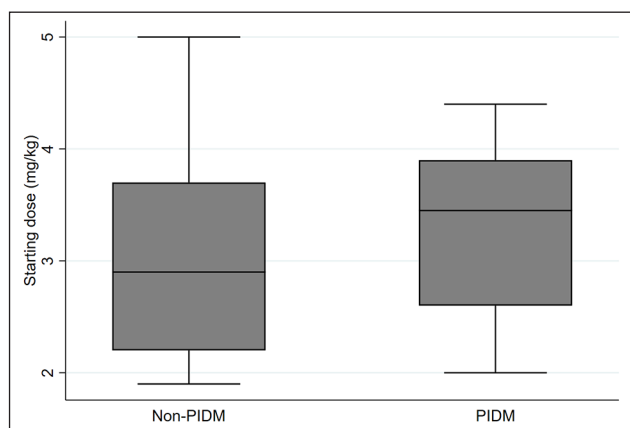


Figure 2 Box plot showing the starting prednisolone dose in the prednisolone-induced diabetes mellitus (PIDM) and non-PIDM groups

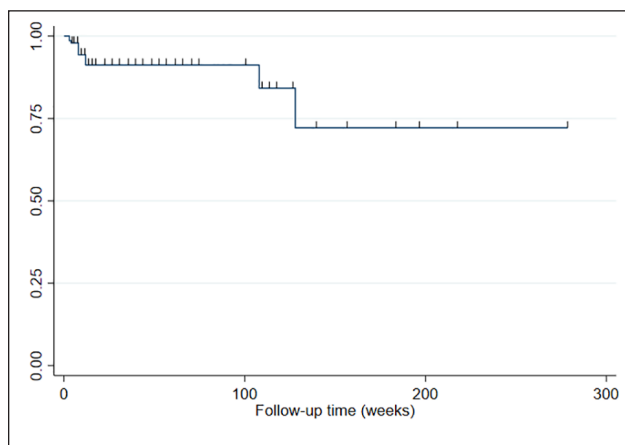


Figure 3 Kaplan-Meier curve showing the time to the development of prednisolone-induced diabetes mellitus in weeks. The vertical lines reflect censored cases

Table 4 Biochemical values in 143 cats in a cohort study of prednisolone-induced diabetes mellitus (PIDM)

Variables (unit; reference interval)	PIDM		Non-PIDM		Overall	
	Median (range)	n	Median (range)	n	Median (range)	n
Blood glucose (mmol/l; 3.4–8.1)	8.7 (5.0–14.4)	10	7.1 (2.54–17.0)	56	7.2 (2.5–17.0)	66
Cholesterol (mmol/l; 2.2–6.7)	3.3 (2.3–8.1)	13	3.2 (1.8–14.4)	107	3.3 (1.8–14.4)	120
ALT (IU/l; 25–130)	57 (26–570)	13	59 (0–1186)	107	58.5 (0–1186)	120
ALP (IU/l; 11–58)	23 (1–305)	13	17 (0–352)	106	17 (0–352)	119

ALT = alanine aminotransferase; ALP = alkaline phosphatase

but significantly higher compared with the proposed prevalence of spontaneous feline DM in first-opinion practices in the UK, which has been reported to be 0.42% and 0.43%.^{2,4} As our study population is from a tertiary referral centre, the prevalence noted in our study might not be representative of the general feline population but is suggestive of an increased risk for cats receiving high doses of prednisolone to develop DM. To the authors' knowledge, no previous studies have reported the prevalence of feline PIDM in client-owned cats, but feline experimental studies have shown the diabetogenic effects of prednisolone. Interestingly, two experimental studies revealed a higher prevalence of hyperglycaemia and glucosuria in laboratory cats receiving prednisolone than compared with our study; Middleton and Watson⁸ showed that 3/6 cats (50%) receiving 2mg/kg/day of prednisolone developed hyperglycaemia after 7 days, and it was shown by Lowe and colleagues⁹ that 2/7 cats (29%) receiving 4.4mg/kg/day developed glucosuria (as a marker of hyperglycaemia) after 28 days. The higher prevalence of hyperglycaemia and glucosuria in these studies likely reflects both differences in study design and marked differences in monitoring compared with our study.

GIDM is well described in humans. Factors including dose, duration of glucocorticoid therapy, cumulative (or absolute) dose, relative potency of the glucocorticoid, age, weight, known reduced insulin sensitivity and family history of diabetes have been found to increase the risk of GIDM.⁶ The starting prednisolone dose was not significantly associated with the development of PIDM in our study; however, a trend could be observed with a higher dose range noted in the PIDM cats (3.5 vs 2.9mg/kg). This is similar to what has been shown in people, where high dose prednisolone therapy is more likely to induce glucose intolerance.¹¹ To avoid the development of GIDM in people, it has been suggested to start in the lower end of the dose range and to reduce the administration frequency to once daily or every other day once the underlying disease is controlled.^{6,12,13} Recently, it has also been shown in dogs that once-daily administration of prednisolone was associated with fewer side effects than twice-daily dosing.¹⁴ Although no clear dose range has been established in cats, it is likely that cats would benefit from a low-end starting dose and probably also reduction in administration frequency to reduce the risk of side effects. The majority of the cats in our study developed PIDM within 3 months

of initiation of therapy, which further supports a dose-dependent relationship.

Another unexplored component, which has been shown to play a role in people,⁶ is cumulative (or absolute) glucocorticoid dose. Long-term, high-dose glucocorticoid (high cumulative dose) use has been associated with the development of GIDM in people and cessation or alternating-day therapy has been shown to be protective (low cumulative dose).¹² A cumulative dose calculation was not performed in this study due to a lack of details in the medical records regarding dose changes during the treatment period. No differences related to duration of therapy were found between PIDM and non-PIDM groups in our study. This, however, could be due to an inadequate study population or that we did not follow enough cases with prolonged prednisolone therapy. Two of the cats in the PIDM group developed DM 108 and 128 weeks after the initiation of prednisolone therapy. Both of these cats were diagnosed with immune-mediated diseases and cessation of prednisolone was not achieved from initiation of prednisolone treatment to the development of diabetes. As such, both cats probably had a high cumulative dose. Prospective studies are needed in cats to assess the effects of prednisolone dose, cumulative dose and frequency of administration on PIDM development.

Relative glucocorticoid potency has been shown to play a role in human GIDM; however, prednisolone was chosen as the glucocorticoid of choice for this study as this was the most commonly used glucocorticoid during the study period in our hospital, with only a very few cases receiving long-term dexamethasone and methylprednisolone. One of the cats in the non-PIDM group, however, developed DM after cessation of prednisolone therapy, but following treatment with methylprednisolone injections. This is consistent with previous experimental studies showing that methylprednisolone is also diabetogenic in cats.^{10,15}

Interestingly, BCS was not significantly associated with the development of PIDM, which is in contrast to what has been shown in cats with spontaneously occurring DM³ and from a pharmacological point of view, where it has been shown that overweight cats have higher plasma prednisolone levels than cats in normal condition.¹⁶ The lack of association noted in our study could be due to a lack of power in the study, compliance in reporting BCS in our medical records or perhaps weight loss prior to presentation secondary to the underlying diseases.

Insulin therapy was only started in 9/14 cats, despite all cats fulfilling criteria for the diagnosis of DM. We were not able to clarify the clinical reasoning for why five of the cats did not receive insulin, but in most cats the prednisolone dose was reduced at the time of DM diagnosis. We suspect that this was adequate to improve glycaemic control in some cats and therefore diminished

the need for insulin treatment. Further studies are needed to determine optimal therapy for cats developing PIDM.

Finally, none of the biochemical abnormalities typically associated with DM were predictive of PIDM. This is likely due to the low number of cases of PIDM; however, the finding of a trend towards an association between glucosuria present prior to therapy and the development of PIDM is interesting. This could reflect impaired glucose tolerance and therefore could serve as a marker to identify cats being predisposed to the development of PIDM, but further studies are needed to conclude on this matter. Based on this study, it would be prudent to advise close monitoring of cats with glucosuria prior to prednisolone therapy for the development of PIDM, especially during the first 3 months of therapy. As with any retrospective study, the lack of standardised treatment, follow-up and a significant number of cases and details lost to follow-up, the conclusions of this study should be interpreted with caution.

Conclusions

Cats requiring high-dose prednisolone therapy should be closely monitored over the first 3 months of therapy for the development of PIDM.

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Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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