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TITLE

Prednisolone-induced diabetes mellitus in the cat: A historical cohort.

Keywords:

Glucocorticoid induced hyperglycaemia, corticosteroid, hyperglycaemia, glucosuria

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 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 prednisolone-induced diabetes mellitus. Twelve out of 14 cats (85.7%) developed diabetes within 3 months of the initiation of therapy.

Conclusion and relevance Cats requiring high-dose prednisolone therapy should be closely monitored over the first 3 months of therapy for development of prednisolone-induced diabetes mellitus.

Introduction

Diabetes mellitus (DM) is one of the most commonly diagnosed endocrine diseases in cats. Diabetes mellitus is characterised by clinical signs including polyuria and polydipsia due to persistent hyperglycaemia and glucosuria as well as polyphagia and weight loss due 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 due to environmental and genetic factors[2]. Environmental factors include obesity[3] and glucocorticoid administration[4]. Glucocorticoids are commonly used drugs in veterinary medicine for 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, amongst others, have been described as risk factors for development of GIDM.

In feline patients, glucocorticoids have been suggested as a predisposing factor for development of DM[4] 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.

Material 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 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 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.
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 prednisolone-induced diabetes mellitus if they had typical clinical signs associated with diabetes mellitus (e.g. polyuria, polydipsia, weight loss and polyphagia) and if they had one of the following criteria fulfilled

1. Hyperglycaemia (>8.1 mmol/L on more than two occasions) in conjunction with glucosuria
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

105 administration and development of PIDM. In addition, serum serum alanine
106 aminotransferase (ALT) and alkaline phosphatase (ALP) activities, serum
107 cholesterol concentration, urine specific gravity, glucosuria measured by urine
108 colorimetric dipstick, blood glucose concentration and body condition score
109 (BCS, scoring from 1 to 9 where 4 and 5 were considered normal) on
110 presentation were noted when available.

111 *Statistical analysis*

112 Data was compiled in Microsoft Excel and imported into Stata 15 (Stata Corp.,
113 College Station, TX), which was used for all statistical analyses. A p-value of
114 <0.05 was considered statistically significant. The continuous variables were
115 assessed graphically and by the Shapiro-Wilks test for normality and are
116 presented as medians (ranges). The categorical variables are described as
117 numbers (percentages). Breed was categorised as pure bred or mixed breed for
118 the statistical analysis. Associations between categorical and continuous
119 variables were explored by the two-sample t-test and Wilcoxon rank sum test
120 for normally and non-normally distributed variables, respectively. Associations

between categorical variables were tested using the $\chi 2$ test or the Fisher 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 development of diabetes in the PIDM group and cats were censored if they died or were lost to follow-up. Box plot 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 (143) cats fulfilled all 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 ($p = 0.895$).

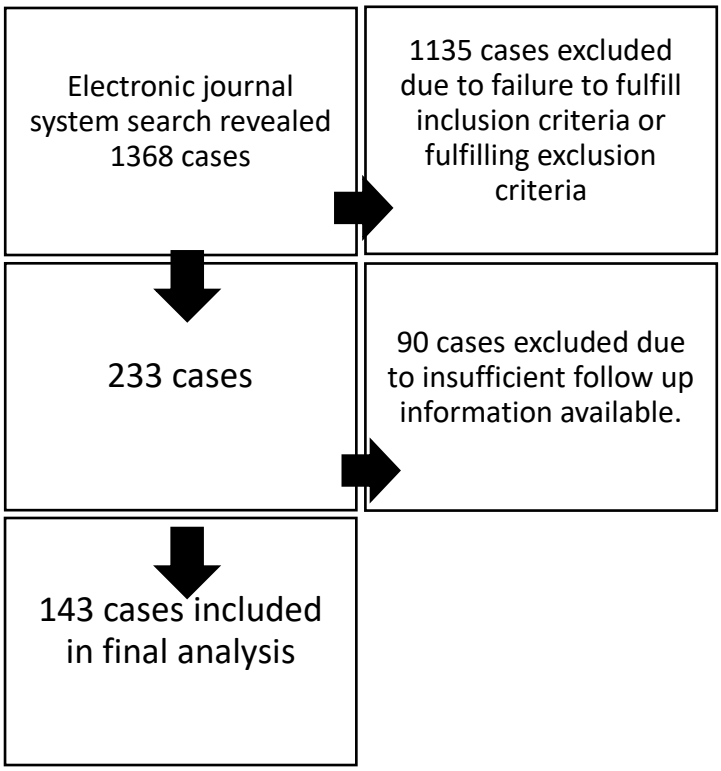

Figure 1: *Inclusion details of 143 cats in a cohort study of prednisolone-induced diabetes mellitus*

Breed	n
Domestic Short hair	82
Domestic Long Hair	10
Persian	8
Bengal	6
Maine Coon	6
British Short Hair	5
Burmese	5
British Blue	4
Siamese	4
Cross Breed	2
Russian Blue	3
Oriental Short Hair	2
Burmilla	1
Chantilly- Tiffany	1
Devon Rex	1
Korat	1
Norwegian Forest Cat	1
Snowshoe	1

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

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 =

166 0.980). BCS was recorded in 100/143 of cases (13/14 of the PIDM group and
167 87/129 of the non-PIDM group), and the median BCS for both groups was 4/9.
168 There were no statistical differences in breed, sex distribution or neuter status
169 between the two groups ($p = 0.238$, $p = 0.385$, $p = 0.467$, respectively; see **table 2**
170 for further details). Immune-mediated haemolytic anaemia and inflammatory
171 bowel disease and dermatological diseases were the three most common
172 underlying diseases treated with prednisolone (**table 3**). Seven (50%) of the cats
173 developing PIDM were treated for immune-mediated haemolytic anaemia, two
174 cats were treated for IBD and two for dermatological diseases. One cat was
175 treated for each of the following diseases: pure red cell aplasia, chronic rhinitis
176 and cholangitis.
177

Variables	PIDM	non-PIDM	Overall
Age in years	7.5 (1.2-13.2)	5.9 (0.6-18.0)	5.9 (0.6-18.0)
Weight in 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)

178 Continuous variables reported as a median (range) and categorical variables as number (%).
179 Body condition score = BCS. Prednisolone-induced diabetes mellitus = PIDM.

180 ***Table 2.*** *Descriptive features of 143 cats in a cohort study of prednisolone-induced diabetes mellitus.*

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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

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

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 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.

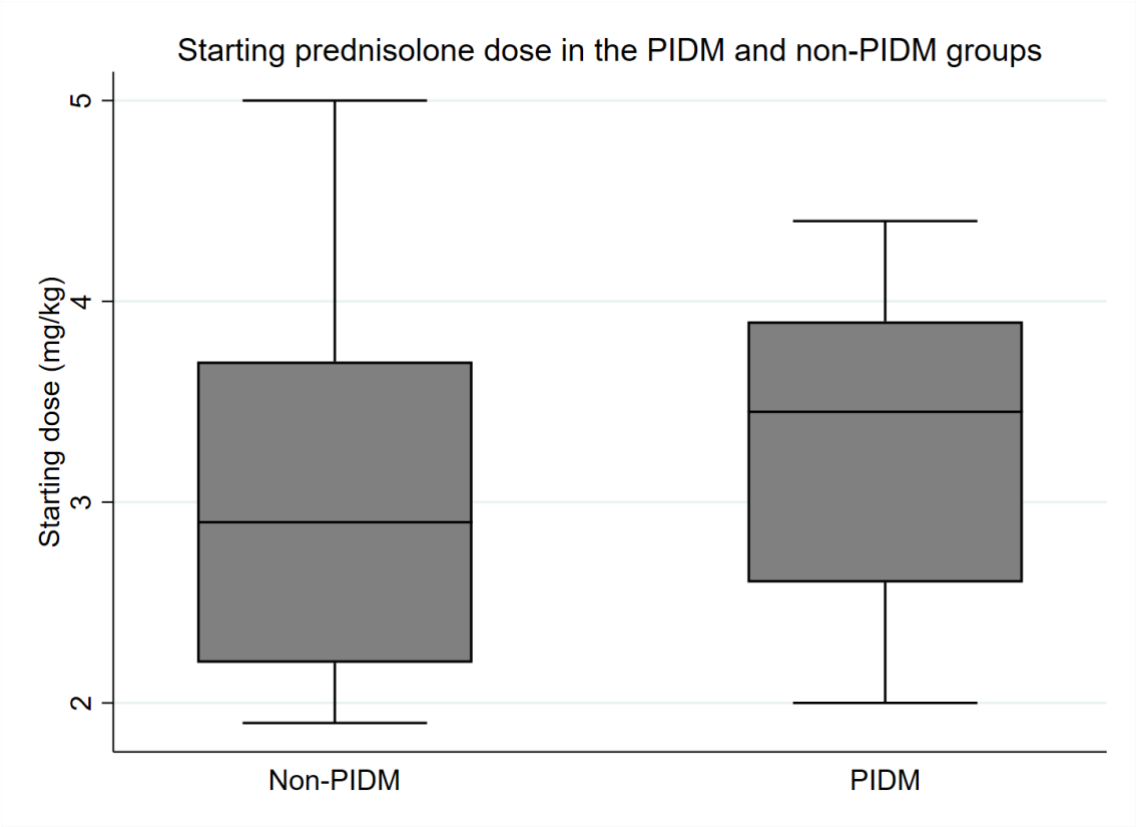
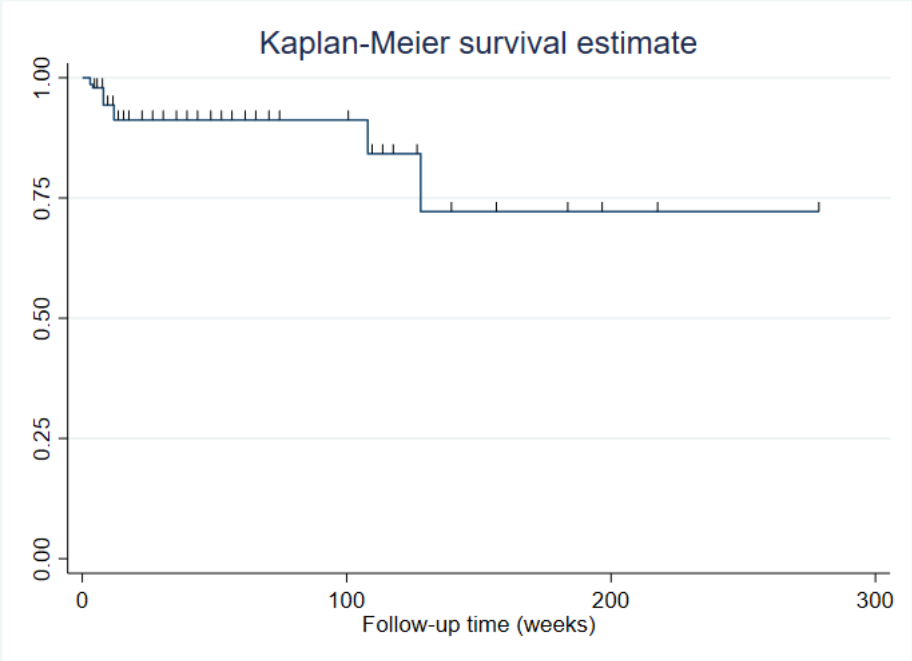


Figure 2: *Box-plot showing the starting prednisolone dose in the PIDM and non-PIDM groups.*

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 1.7mg/kg and from 0.25mg/kg to 2mg/kg

211 respectively) after being diagnosed with a relapse of their underlying immune-
212 mediated disease (thrombocytopenia and anaemia) after 108 and 128 weeks
213 being on prednisolone, respectively.



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

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218 The assessed clinicopathological values, measured prior to prednisolone
219 therapy, are summarised in **table 5**. Neither blood glucose concentration, serum
220 cholesterol concentration, serum ALP nor ALT activities were associated with

221 the development of PIDM (p = 0.180, 0.623, 0.418 and 0.513, respectively).

222 Urinalysis prior to prednisolone treatment was available in 9/14 cats of the

223 PIDM group and 72/129 cats of the non-PIDM group. Glucosuria was detected

224 in 4/9 (44.4%) and 11/72 (15.3%) of the cats, respectively (p = 0.056).

	PIDM		non-PIDM		Overall	
Variables (units; reference intervals)	Median (range)	n	Median (range)	n	Median (range)	n
Blood glucose (mmol/l; 3.4 - 8.1)	8.7 (5.0-14.4)	1 0	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)	1 3	3.2 (1.8-14.4)	10 7	3.3 (1.8-14.4)	12 0
ALT (IU/l; 25-130)	57 (26-570)	1 3	59 (0-1186)	10 7	58.5 (0-1186)	12 0
ALP (IU/l; 11-58)	23 (1-305)	1 3	17 (0-352)	10 6	17 (0-352)	11 9

225 ALT = alanine aminotransferase. ALP = alkaline phosphatase.

226 ***Table 4.*** *Biochemical values in 143 cats in a cohort study of prednisolone-induced diabetes mellitus.*

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Discussion

The prevalence of PIDM was 9.7% in our study. This is lower than the reported prevalence of 18.7% in people[6], but significantly higher compared to 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 diabetes mellitus. 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 to our study; Middleton and Watson[8] showed that three out of six cats (50%) receiving 2mg/kg/day of prednisolone developed hyperglycaemia after 7 days and it was shown by Lowe and colleagues[9] two out of seven 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 to 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 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 2.9 mg/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 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 less 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 development of GIDM in people and that cessation or alternating-day therapy is protective (low cumulative dose)[12]. Cumulative dose calculation was not performed in this study due to lack of details in medical records regarding dose changes during the treatment period. No differences related to duration of therapy was found between PIDM and non-PIDH 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

276 the PIDM group developed diabetes mellitus 108 and 128 weeks after initiation
277 of prednisolone therapy. Both of these cats were diagnosed with immune-
278 mediated diseases and cessation of prednisolone was not achieved from
279 initiation of prednisolone treatment to the development of diabetes. As such,
280 both cats probably had a high cumulative dose. Prospective studies are needed
281 in cats to assess the effects of prednisolone dose, cumulative dose and
282 frequency of administration on PIDM development.

283 Relative glucocorticoid potency has been shown to play a role in human GIDM,
284 however prednisolone was chosen as the glucocorticoid of choice for this study
285 as this was the most commonly used glucocorticoid during the study period in
286 our hospital, only with a very few cases receiving long-term dexamethasone
287 and methylprednisolone. One of the cats in the non-PIDM group, however,
288 developed diabetes mellitus after cessation of prednisolone therapy, but
289 following methylprednisolone injections treatment. This is consistent with
290 previous experimental studies showing that methylprednisolone also is
291 diabetogenic in cats[10,15].

Interestingly, BCS was not significantly associated with development of PIDM, which is in contrast to what has been shown in cats with spontaneously occurring diabetes mellitus[3] and from a pharmacological point of view, where it has been shown that overweight cats have higher plasma prednisolone levels than normal conditioned cats[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 due to 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 diabetes mellitus. We were not able to clarify the clinical reasoning 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 development of PIDM is interesting. This could reflect impaired glucose tolerance and therefore could serve as a marker to identify cats being predisposed to 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 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.

Conclusion

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

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Author note

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Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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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 animals described in this work for the procedure(s) undertaken. No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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