Case Report

Diabetes mellitus remission in a cat with pituitary-dependent hyperadrenocorticism after trilostane treatment

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Abstract

Case summary An 8-year-old male neutered Persian cat was presented with polyuria, polydipsia, polyphagia and muscle weakness associated with a 7 month history of diabetes mellitus (DM). The cat had initially been treated with neutral protamine Hagedorn (NPH) insulin 2 U q12h, followed by porcine lente insulin 2 U q12h and, most recently, 3 U glargine insulin q12h, without improvement of clinical signs. The cat also suffered from concurrent symmetrical bilateral alopecia of thorax and forelimbs, abdominal distension and lethargy. Hyperadrenocorticism (HAC), specifically pituitary-dependent HAC, was suspected and confirmed through abdominal ultrasonography demonstrating bilateral adrenal enlargement, and a low-dose dexamethasone suppression test using 0.1 mg/kg dexamethasone intravenously. Triostane treatment (initially 10 mg/cat PO q24h then increased to 10 mg/cat PO q12h) was started and insulin sensitivity gradually improved, ultimately leading to diabetic remission after an increased in triostane dose to 13 mg/cat PO q12h, 14 months after the DM diagnosis and 7 months after the initiation of triostane therapy.

Relevance and novel information DM in cats with HAC is a difficult combination of diseases to treat. To our knowledge this is the first reported case of diabetic remission in a feline patient with HAC as a result of treatment with triostane. Further work should focus on whether fine-tuning of triostane-treatment protocols in cats with concurrent DM and HAC could lead to a higher proportion of diabetic remissions in this patient group.

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Case description

An 8-year-old male neutered Persian cat, weighing 3 kg, with a body condition score of 3/5 was referred to a dedicated veterinary endocrinology clinic (PetEndocrine, Brazil) for uncontrolled diabetes mellitus (DM). The cat had initially been treated with neutral protamine Hagedorn (NPH) insulin (up to 2 U q12h SC [Humulin N; Lilly]), was then switched to porcine lente insulin (up to 2 U q12h SC [Caninsulin; MSD]) and, most recently, the cat had been receiving 3 U glargine insulin (q12h SC [Lantus; Aventis]). There had not been any significant improvement in diabetic clinical signs and the cat continued to suffer from polyuria and polydipsia, polyphagia, muscle weakness and lethargy.

On physical examination, the cat displayed abdomino distension, fragile/thin skin and symmetrical bilateral alopecia predominantly affecting the thorax and limbs (Figure 1). The clinical signs and lack of response to treatment gave rise to a suspicion of concurrent
hyperadrenocorticism (HAC). Blood work and urine analysis results are shown in Table 1. A serum fructosamine concentration suggested good control (369 µmol/l; reference interval [RI] for good diabetic control established by the employed laboratory 350–400 µmol/l). However, given the persistence of clinical signs and the results of serial blood glucose evaluation (Table 1, Figure 2), the glargine dose was increased to 4 U q12h SC. One week later, a low-dose dexamethasone suppression test (LDDST; using 0.1 mg/kg dexamethasone IV) was conducted, the results of which proved compatible with pituitary-dependent HAC (PDH): basal cortisol 143.7 nmol/l (RI 10–138 nmol/l), 4 h post-dexamethasone 64.6 nmol/l and 8 h post-dexamethasone 49.4 nmol/l (normal response <38 nmol/l). Additionally, bilateral adrenomegaly was present on abdominal ultrasonography (US), further supporting this diagnosis (Figure 3). The liver appeared a little heterogeneous on US, whereas the gall bladder showed thickened walls (0.25 cm), suggesting cholecystitis.

Treatment with trilostane (Vetoryl; Dechra) at a dose of 10 mg q24h PO was initiated. Over the next 2 weeks, the cat showed weight gain and increased activity, as well as normalization of interaction with the owners. Additionally, glycemic control improved, as demonstrated by subsequent resolution of diabetic signs, as well as serial blood glucose assessment (Figure 2). Fourteen days after the start of therapy, an adrenocorticotropic hormone (ACTH) stimulation test was performed 6 h after trilostane administration, using 0.125 mg/cat intravenous synthetic ACTH (Synacthen; Novartis). Based on a post-ACTH cortisol concentration of 136.8 nmol/l (suggested target range 55–165 nmol/l), the trilostane dose was increased to 10 mg q12h PO, in an effort to optimize glycemic and HAC control. One month later (40 days after starting trilostane), the cat was once again presented, this time with clinical signs compatible with hypoglycemia (prostration), at which stage a blood glucose of 2.4 mmol/l was recorded. Furthermore, serum fructosamine concentration was consistent with chronic hypoglycemia (257 µmol/l; RI for possible chronic hypoglycemia <300 µmol/l). The insulin dose was therefore reduced to 2 U q12h and an ACTH stimulation test was performed. The 1 h post-ACTH cortisol concentration (146.2 nmol/l) rendered hypocortisolism contributing to the hypoglycemia unlikely. The trilostane dose was therefore kept unaltered (10 mg/cat q12h).

Two months later (100 days after starting trilostane) the cat was reported to show no clinical signs of DM, demonstrated an increased weight of 3.4 kg, complete fur re-growth (Figure 4) and fair control of blood glucose concentrations. This prompted a further decrease in insulin dose to 1 U q12h SC. The post-ACTH cortisol concentration obtained at this point suggested effective adrenal suppression (116.4 nmol/l). However, the cat was also reported to show behavioral changes, including aggression, vocalization at night, hypersexuality and increased libido. After 200 days of trilostane treatment, the post-ACTH cortisol concentration was 137.1 nmol/l (tests performed 8 h after trilostane administration); trilostane was readjusted to the dose of 13 mg q12h PO by compounding capsules at a veterinary pharmacy certified by the Brazilian Ministry of Agriculture, Livestock, and Food. Given the lack of clinical signs of DM and the serum fructosamine concentration (Table 1), the insulin dose was reduced to 0.5 U q12h SC. Two weeks later, the cat showed absence of glycosuria and once again a serum fructosamine concentration was consistent with chronic hypoglycemia (205 µmol/l; RI for possible chronic hypoglycemia <300 µmol/l), prompting complete insulin withdrawal and subsequent testing for diabetic remission. To test for diabetic remission, the cat was closely monitored by its owners for the recurrence of clinical signs, as well as regular blood glucose tests for the next 4 weeks. Diabetic remission was confirmed; monitoring of the cat was continued for the following 20 months. Relapse of DM did not occur.

**Discussion**

This report describes the first case of diabetic remission in a cat with underlying HAC while being treated with

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**Figure 1** (a) Emaciation, muscle loss, unkept haircoat and alopecia. (b) Fragile thin inelastic skin. (c) Bilateral symmetrical alopecia, unkept haircoat, and potbellied abdomen
Table 1  Serum biochemical parameters and urinalysis of the cat at initial consultation and during follow-up visits

|                     | First consult | 14 days | 40 days | 100 days | 200 days | 214 days | 274 days | 574 days | RI          |
|---------------------|--------------|---------|---------|----------|----------|----------|----------|----------|-------------|
| Trilostane dose (mg/cat) | 0           | 10 (q24h) | 10 (q12h) | 10 (q12h) | 10 (q12h) | 13 (q12h) | 13 (q12h) | 13 (q12h) |             |
| Glargine dose (U/cat)    | 3 (q12h)    | 4 (q12h) | 4 (q12h) | 2 (q12h) | 1 (q12h) | 0.5 (q12h) | –         | –         |             |
| Albumin (g/l)          | 26.1        | 26.7    | 24      | 22       | 21       | 24       | 28       | 23.3     | 21–39       |
| ALT (µ/l)              | 72          | 183     | 114     | 83       | 85       | –        | 79       | 67       | 6–83        |
| ALP (µ/l)              | 134         | 30      | 160     | 60       | 60       | –        | 46       | 28       | 25–93       |
| Fructosamine (µmol/l)  | 369         | 283     | 257     | 228      | 210      | 205      | 244      | 272      | 219–340     |
| Creatinine (µmol/l)    | 106.9       | –       | –       | –        | 132.6    | 119.3    | 106.1    | 108.7    | 53–159.1    |
| Urea (mmol/l)          | 16.7        | –       | –       | –        | 21.43    | 17.5     | –        | 22.5     | 3.57–21.43  |
| Triglycerides (mmol/l) | 2.21        | –       | –       | –        | –        | –        | –        | 0.62     | 0.56–1.13   |
| Cholesterol (mmol/l)   | 4.93        | –       | –       | –        | –        | –        | –        | 2.35     | 2.45–3.36   |
| Potassium (mmol/l)     | –           | 4.2     | 4       | 4        | 4.2      | –        | –        | 4.2      | 3.80–4.51   |
| Sodium (mmol/l)        | –           | 147     | 145     | 145      | 142      | –        | –        | 142      | 145–157     |
| USG                   | 1.020       | 1.030   | 1.025   | 1.030    | 1.020    | 1.020    | –        | 1.020    | ≥1.035      |
| UP:CR                 | –           | 0.17    | 0.19    | 0.17     | 0.2      | 0.14     | –        | 0.44     | <0.4        |
| Glycosuria (mg/dl)     | 2000        | 2000    | 1000    | 0        | 0        | 0        | –        | 0        | 0           |
| Glargine adjustments (U/cat) | ↑ 4 U (q12h) | – | ↓ 2 U (q12h) | ↓ 1 U (q12h) | ↓ 0.5 U (q12h) | Glargine withdrawal | – | – | – |
| Trilostane adjustments (mg/cat) | – | ↑ 10 (q12h) | – | – | ↑ 13 (q12h) | – | – | – |

The time points represent days in treatment with trilostane. Moreover, trilostane and glargine dose in use at each time point, and adjustments made based on cat’s clinical evaluation are shown. RI = reference interval; ALT = alanine aminotransferase; ALP = alkaline phosphatase; USG = urine specific gravity; UP:CR = urinary protein:creatinine ratio; ↑ = dose increase to; ↓ = dose reduction to.
trilostane. Given that HAC is a difficult disease to treat and the treatment effect of trilostane, specifically, has been noted to be variable in diabetic cats with HAC,\textsuperscript{1,2} the current report highlights that satisfactory results can be obtained in individual cats.

Naturally occurring HAC is an uncommon disorder in cats, arising from either adrenocortical (ACTH-independent HAC) or pituitary hyperfunction leading to excess cortisol production; PDH due to corticotroph adenoma is thought to be the most usual form.\textsuperscript{2–7} Excess cortisol production by adrenal glands induces insulin antagonistic and catabolic effects.\textsuperscript{2,5} Specifically, the excessive exposure to glucocorticoids has been associated with DM in cats and dogs.\textsuperscript{5–11} Cats seem particularly vulnerable to HAC-induced DM with 80% of HAC cats developing secondary DM; in contrast only 8–16% of dogs with HAC have concurrent DM.\textsuperscript{5,9,12,13}

The described case showed characteristics previously associated with feline HAC-induced DM, including insulin resistance, dermatological changes such as symmetrical alopecia, as well as some non-specific clinical pathological changes such as hypercholesterolemia, hypertriglyceridemia and increased alkaline phosphatase.\textsuperscript{1,2,10,11} Although the condition is thought to be relatively rare, the presence of these more characteristic clinical signs in conjunction with a DM diagnosis should give rise to a suspicion of HAC in cats.\textsuperscript{14} The most commonly recommended diagnostic tests for HAC in cats include the LDDST (in cats, using a dose of 0.1 mg/kg of dexamethasone), the ACTH stimulation test (though suggested to be lacking in sensitivity) and the urine cortisol:creatinine ratio (though suggested to be lacking specificity).\textsuperscript{7,14,15}

In this case, diabetic remission (defined as absence of clinical signs suggestive of DM, normal blood glucose and fructosamine concentrations, while not receiving exogenous insulin for at least 1 month)\textsuperscript{16} is thought to have been achieved by a reduction of insulin resistance through reduction of endogenous cortisol concentrations, as well as concurrent recovery of beta cells function, through reduction of glucotoxicity (structural and functional damage in pancreatic beta cells and the target tissues of insulin caused by chronic hyperglycemia).\textsuperscript{9} This would, perhaps, be similar to the situation in cats with DM associated with previous exogenous glucocorticoid administration. Interestingly, diabetic cats with a previous history of exogenous glucocorticoid treatment have been shown to benefit from a greater chance of diabetic remission.\textsuperscript{16} This suggests that effective treatment of HAC in diabetic cats could

\begin{figure}
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\includegraphics[width=\textwidth]{Figure2}
\caption{Home-generated serial blood glucose measurements before diabetic remission. The curves are shown in relation to glargine insulin dose modifications and days on trilostane treatment. All curves started at midday and finished at midnight.}
\end{figure}
also carry such increased potential of diabetic remission. Diabetic remission through medical pituitary inhibition has also recently been shown to be possible in another form of pituitary-induced feline secondary DM, hypersomatotropism-induced DM. Gostelow et al described 25% of cats with this condition to show diabetic remission through use of the pituitary inhibitor pasireotide (a somatostatin analogue [Signifor LAR; Novartis]).

In cases of type 2 feline DM, diabetic remission is suggested to occur most commonly within the first 6 months after diagnosis and more rarely thereafter. Diabetic remission of the cat in this report occurred 14 months after diagnosis. This is, however, not a contradiction, as the cat’s DM was of a different kind, occurring secondarily to HAC and thus likely more amenable to remission, as long as the underlying inducing disease, HAC, is treated effectively. The late occurrence of remission after

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**Figure 3** Ultrasonographic appearance showing bilateral enlargement of the adrenal glands. (a) Left (L) adrenal longitudinal section (1.41 × 0.71 cm). (b) Left adrenal transverse (transv) section (0.68 × 0.88 cm). (c) Right (R) adrenal transverse section (0.76 × 1.01 cm). (d) Right adrenal longitudinal section (1.36 × 0.8 cm)
months of trilostane treatment emphasizes the need for careful monitoring of insulin-treated diabetic cats with underlying HAC treated with trilostane, as iatrogenic hypoglycemia can pose a danger if the onset of remission is missed. Indeed, in the current case, it would have been indicated to have checked the cat’s glucose concentrations more frequently and/or for the owner to have conducted more intense monitoring at home (home blood glucose or urine glucose monitoring); unfortunately, this was not possible for the owner in question. Moreover, this cat might have been able to stop insulin even earlier, once normal fructosamine values and absence of glycosuria were detected at some time points before insulin withdrawal.

The reason(s) why this particular case achieved diabetic remission, whereas other, seemingly similar, cats do not remain(s) unknown. Trilostane treatment was not started more promptly than in other reported cases; the employed trilostane dose was not significantly different nor were the attained post-ACTH cortisol concentrations superior than in previously reported cases. Diabetic remission has previously been suggested to occur more frequently in glargine-treated diabetic cats, although this was subsequently questioned in a systematic review of the topic, particularly given the small size of that study and several included biasing factors. Additionally, cats previously treated with both trilostane and glargine have failed to enter diabetic remission. Nevertheless, remission-associated factors that should be considered are the influence of trilostane frequency and dose, target post-ACTH cortisol concentrations and the influence of the concurrent insulin treatment regimen.

Conclusions
This report details the first case of diabetic remission in a cat with HAC treated with trilostane. Further work should focus on whether fine-tuning of trilostane-treatment protocols in patients with DM-associated with HAC could lead to a higher proportion of cats achieving diabetic remission. Treatment success should be compared to alternative treatment options, including hypophysectomy.

Conflict of interest
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