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Diabetes mellitus remission in three cats with hypersomatotropism after cabergoline treatment

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Abstract

Case summary Three diabetic cats presented with polyuria, polydipsia, polyphagia and poor glycemic control. Cat 1 displayed prognathia inferior and had a body condition score (BCS) of 4/5; cat 2 had a BCS of 5/5; and cat 3 had broad facial features. Serum insulin-like growth factor 1 concentrations were compatible with hypersomatotropism in cat 1 and cat 2 (>1500 ng/ml and 1200 ng/ml, respectively) and just below the cut-off of 1000 ng/ml (947 ng/ml) in cat 3; in this last cat diagnosis was further supported by the presence of pituitary enlargement on MRI. Oral cabergoline (10 µg/kg q48h) was initiated. Insulin requirements progressively reduced, as evidenced by daily blood glucose monitoring and weekly blood glucose curves. Diabetic remission occurred in all three cats between the second and third months of cabergoline treatment. At the time of writing, remission has persisted thus far (cat 1: 23 months; cat 2: 14 months; cat 3: 38 months).

Relevance and novel information To our knowledge, these are the first reported cases of diabetic remission in cats with hypersomatotropism after cabergoline treatment, despite previous reports of this being an ineffective treatment. Further work is indicated to determine why some cats do, and others do not, respond to this treatment.

Keywords: Diabetes mellitus remission; hypersomatotropism; acromegaly; cabergoline; insulin resistance

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Case description

Three cats (all domestic shorthair neutered males; cat 1 was 15 years old, cat 2 was 7 years old and cat 3 was 13 years old [Table 1]) were referred to the Endocrine Unit of the Hospital School of the Faculty of Veterinary Sciences (University of Buenos Aires, Argentina) with polyuria, polydipsia, polyphagia and poor glycemic control of diabetes mellitus (DM). The cats were receiving a commercial diet for diabetic cats and increasing doses of glargine (Lantus; Sanofi-Aventis). Despite the increases in insulin doses (cat 1: 1.1 IU/kg q12h; cat 2: 0.9 IU/kg q12h; cat 3: 2 IU/kg q12h), no remarkable improvements were observed in clinical signs, fasting glycaemia and serum fructosamine concentration. Only one cat (cat 3) had experienced weight loss since the onset of DM. All cats had been treated for DM for 2–3

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Table 1 Age, weight, insulin dose and clinical findings in three diabetic cats with hypersomatotropism before cabergoline treatment

	Age (years)	Weight (kg)	Insulin dose (U/q12h)	Clinical findings
Cat 1	15	7	8	Mild prognathia inferior and overweight (BCS 4/5)
Cat 2	7	11	10	Overweight (BCS 5/5)
Cat 3	13	3.5	7	Mild broad facial features and widening of interdental space

BCS = body condition score

**Figure 1** Clinical aspects of three diabetic cats with hypersomatotropism: (a) cat 1, (b) cat 2 and (c) cat 3

months by their veterinarians. Likewise, none of them had been treated with glucocorticoids or progestagens.

On physical examination, the clinical findings were mild prognathia inferior and a body condition score (BCS) of 4/5 in cat 1, a BCS of 5/5 in cat 2, and mild broad facial features and mild widening of interdental spaces in cat 3 (Table 1; Figure 1). Blood work and urinalysis results were normal, except for the presence of glycosuria and elevated serum fructosamine concentrations observed in all three cats (Table 2; Figure 2), hyperproteinemia (9.2 g/dl; reference interval [RI] 5–7) and hypercholesterolemia (8.5 mmol/l; RI 2.5–3.7) observed in cat 1. Spontaneous hypercortisolism and hyperthyroidism were ruled out as there were no clinical signs of these diseases, and documentation of normal total thyroxine and a urinary cortisol:creatinine ratio below the RI made a diagnosis of hypercortisolism unlikely. For completeness, feline immunodeficiency virus (FIV) and feline leukemia virus (FELV; immunochromatographic

assay [Speed DUO FeLV-FIV; Virbac]) were negative.¹ Hypersomatotropism was suspected and confirmed by measurement of serum insulin-like growth factor 1 (IGF-1; commercially available RIA [Immuno-Biological Laboratories]) in all cats and also MRI in one cat (Table 2). Serum IGF-1 concentrations were >1500 ng/ml in cat 1 and 1200 ng/ml in cat 2, with values >1000 ng/ml considered indicative of hypersomatotropism. In cat 3, serum IGF-1 concentration was 947 ng/ml; in this case, MRI confirmed enlargement of the pituitary gland (5.7 mm width × 4.5 mm height [normal in mesocephalic cats: up to 4.7 ± 0.31 mm width and up to 3.1 ± 0.25 mm height according to Häußler et al²]) (Figure 3).

An oral dose of 10 µg/kg cabergoline (Dostinex; Pfizer) q48h was prescribed.³ Monitoring of clinical signs, as well as home blood glucose monitoring, was performed by the owners and the veterinary team to try and make appropriate adjustments to the insulin dose (glucose measured with a FreeStyle Optium glucose

Table 2 Serum insulin-like growth factor (IGF)-1 concentrations before and during cabergoline treatment in three diabetic cats with hypersomatotropism

	IGF-1 (ng/ml)*			
	Diagnosis	Cabergoline treatment		
		3 months	6 months	12 months
Cat 1	>1500	>1500	>1500	>1500
Cat 2	1200	1284	1173	1100
Cat 3	947	436	425	1210

*Reference interval <800 ng/ml

meter [Abbott]). In the first week of cabergoline treatment, there were no remarkable changes in blood glucose values or clinical signs in any of the cats. During this first week, blood glucose concentrations prior to injection remained above 20 mmol/l and serial blood glucose measurements still suggested presence of insulin resistance (IR). In the following weeks, the cats became less polyuric, polydipsic and polyphagic. The owners also had to decrease the insulin dose progressively owing to the documentation of lower blood glucose concentrations, with pre-insulin values of 4.4–6.7 mmol/l, values that had not been documented since the start of DM treatment. Additionally, each blood glucose curve showed the necessity to reduce the insulin dose progressively (Figure 4). During this process, none of the cats showed clinical signs of hypoglycemia.

Between the second and third months of cabergoline treatment, insulin administration was no longer necessary in any of the cats (Figures 2 and 4). Clinical signs of DM had completely disappeared and serum fructosamine concentrations normalized in the third month (cat 1: 340 $\mu\text{mol/l}$; cat 2: 306 $\mu\text{mol/l}$; cat 3: 304 $\mu\text{mol/l}$ [RI 200–360]; Figure 2). Similarly, glycosuria was not observed after withdrawing insulin. DM remission has persisted until the time of writing, with extensive follow-up (cat 1: 23 months; cat 2: 14 months; cat 3: 38 months). A clinically relevant decrease of serum IGF-1 concentrations was documented in cat 3 at months 3 and 6; however, by month 12 the IGF-1 value had returned to pre-cabergoline treatment concentrations (Table 2). In cats 1 and 2, a decrease in serum IGF-1 concentrations was not documented. No side effects were observed during the entire study. Cabergoline treatment was continued in all cats during the whole observation period (including the extensive follow-up).

In cat 2, after 6 months of cabergoline treatment, the cat intermittently experienced mild hypoglycemia (fasting glycemia between 2.8 and 3.3 mmol/l) without clinical signs. Therefore, to avoid clinical consequences of

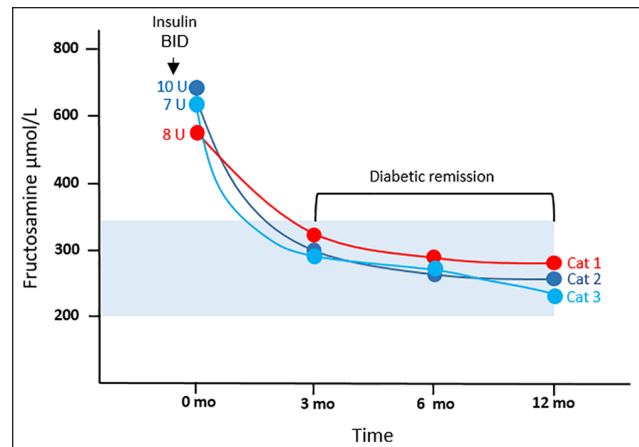


Figure 2 Serum fructosamine concentrations before and during treatment with cabergoline in three diabetic cats with hypersomatotropism. Between the second and third months of cabergoline treatment, diabetic remission was achieved in these cats

hypoglycemia, the dosing interval of cabergoline was progressively increased. First, cabergoline was administered every 3 days. Fasting glycemia always registered concentrations <6.7 mmol/l and the reappearance of clinical signs of DM was not observed at any time with the new regimen. After 2 weeks, cabergoline was administered every 4 days and eventually every 7 days. At the time of writing, fasting blood glucose concentrations ranged between 4.4 and 6.6 mmol/l, and the cat continues to receive a single dose of cabergoline (10 $\mu\text{g/kg}$) every 7 days.

Discussion

In the three cases presented in this report, cabergoline seemed effective in progressively reducing insulin requirements until achieving diabetic remission. To our knowledge, this is the first report to describe cases of DM remission in cats with hypersomatotropism after cabergoline treatment.

Spontaneous hypersomatotropism, or acromegaly, is a chronic metabolic disease caused by hypersecretion of growth hormone (GH). In cats, it is mainly caused by a functional adenoma of the pituitary gland (somatotrophinoma). Hypersomatotropism is often characterized by the presence of DM, which is sometimes insulin-resistant in nature. Additionally, in about a quarter of cats, progressive overgrowth of soft tissues, bones and viscera can be noted, and cardiovascular complications can also occur.⁴ It is estimated that 17–25% of diabetic cats in Europe have hypersomatotropism.^{5,6} All three cats showed elevated serum IGF-1; values >1000 ng/ml in the UK have previously been associated with a 95% positive predictive value of the presence of hypersomatotropism.⁴ Initially, cat 3 was below this cut-off value;

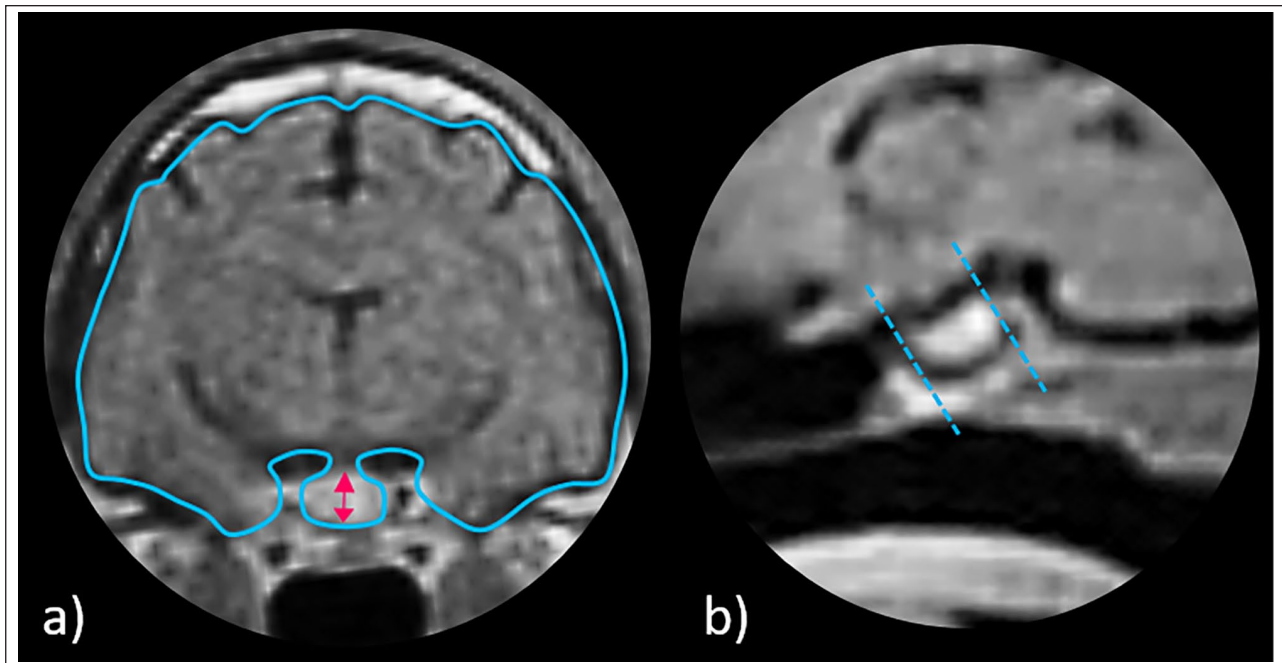


Figure 3 T1-weighted MRI of the sellar region post-gadolinium. Enlargement of the pituitary gland was observed on the MRI of this cat (cat 3): 5.7 mm width \times 4.5 mm height. (a) Cross section, pituitary height: brain area ratio = 0.32; (b) sagittal section

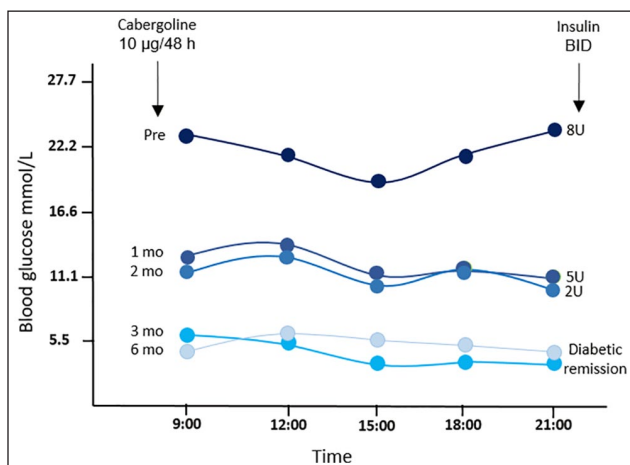


Figure 4 Home-generated serial blood glucose curves before and during cabergoline treatment (cat 1). All curves started in the morning and finished at evening. Pre = before treatment with cabergoline; mo = month

nevertheless, the IGF-1 was above the laboratory RI and values >1000 ng/ml were recorded eventually; additionally, a pituitary enlargement was documented in this cat on MRI. As hypersomatotropic cats can have a pituitary microadenoma or hyperplasia, finding a pituitary enlargement is not required to substantiate a diagnosis of hypersomatotropism;⁵ instead, the clinical ante-mortem diagnosis can be made on the basis of the combination of clinical and hormonal evidence of GH excess.

Feline diabetic remission is defined as the absence of clinical signs of DM, normal blood glucose and fructosamine concentrations without medical antidiabetic therapy, for a minimum of 28 days.^{7,8} All cats in this report fulfilled these criteria. Feline diabetic remission has previously been described in acromegalic cats treated with trans-sphenoidal hypophysectomy, radiotherapy and pasireotide.^{9–11}

Cabergoline is a long-acting dopamine agonist (DA), with a high affinity for dopamine receptor 2 (D2R). In human medicine, DAs were the first drugs used in acromegaly.¹² Used as a monotherapy, cabergoline is effective in normalizing serum IGF-1 concentrations and reducing tumor size in one-third of patients.¹³ When a somatostatin analogue fails to control acromegaly, cabergoline add-on therapy normalizes serum IGF-1 concentrations in 50% of cases.¹³ In veterinary medicine, cabergoline is frequently used as a treatment for pseudopregnancy in dogs.¹⁴ In Argentina, it is also used in dogs with pituitary-dependent hypercortisolism (PDH), reducing adrenocorticotropic hormone (ACTH) production and pituitary adenoma proliferation.¹⁵ We previously published the first report of cabergoline treatment of hypersomatotropism in cats with successful results.³ Despite the number of cases and the brief follow-up, serum IGF-1 concentrations and IR decreased significantly in those three cases.³ Interestingly, in a study from the UK, cabergoline was not effective in controlling DM, lowering IGF-1 and fructosamine, or reducing insulin doses in eight diabetic cats with

hypersomatotropism.¹⁶ It is currently unclear why some cats do respond to cabergoline and other cats do not. Hypotheses include the existence of various subpopulations of somatotrophinomas with varied dopamine receptor expression and agonist affinity, regional variants of hypersomatotropism or cat breeds, different dosing regimens and different commercial preparations of cabergoline used in the two studies.^{3,16}

The expression of D2R has been demonstrated in the pituitary gland of cats with hypersomatotropism. In addition, a moderate negative correlation between pituitary size and D2R expression has been described.¹⁷ In this report, we only performed intracranial imaging in one cat (imaging was declined by owners in the other cats); the pituitary tumor was found to be relatively small in this cat. In line with the findings of Scudder et al,¹⁷ it could be hypothesized that this small size made the somatotrophinoma more likely to respond to cabergoline treatment.

The three cats in this report had a gradual reduction in their insulin requirements with cabergoline treatment, leading to diabetic remission. Two of the cases also presented with subtle acromegalic features, which were not corrected with cabergoline. Cabergoline was not effective in reducing serum IGF-1 concentrations (and therefore probably not GH concentrations). Only one cat had a temporary reduction in serum IGF-1 concentration, which had returned to similar pre-cabergoline treatment concentrations at month 12 (Table 2). It should therefore be emphasized that cabergoline failed to control the hormonal dysregulation completely; therefore, other consequences of GH and IGF-1 excess could continue to take place. Most worryingly, hypertrophic changes to the myocardium, which were not assessed, could therefore lead to future cardiovascular disease and death. Nevertheless, cabergoline treatment did enable diabetic control and ultimately remission, and thus enable improved quality of life of the cats and their owners.

The mechanism by which cabergoline controls DM is not yet understood. Considering that all cats achieved diabetic remission without seemingly reducing serum IGF-1 concentrations is interesting. Nevertheless, this phenomenon has also been reported with radiotherapy.¹⁰ A partial explanation could be that IGF-1 concentrations do not correlate totally with GH concentrations; a reduction in GH could therefore occur without it showing up alongside reductions in IGF-1, especially if the measured concentration of IGF-1 was above the measurable range of the assay (in this case >1500 ng/ml). Another explanation could be that cabergoline affects glycemic control by a mechanism independent of the somatotrophic axis. In animal models, DAs regulate metabolic pathways in the central nervous system and promote insulin sensitivity by decreasing hypothalamic stimulation of hepatic glucose production and lipid generation.^{18,19} Additionally, effects on prolactin (PRL) secretion could

play a role. The role of PRL in glucose metabolism is controversial. Several studies have shown that PRL induces IR, weight gain and food intake, favoring the development of type 2 DM.^{20,21} Other studies showed that PRL has effects on pancreatic beta-cell mass and reduces the threshold for glucose-stimulated insulin secretion, favoring a protective effect against type 2 DM.^{22,23} Interestingly, in humans, cabergoline has been shown to improve glycemic control and to reduce HbA1c concentrations.^{24,25} Likewise, cabergoline has been reported to improve metabolic parameters (total cholesterol, triglycerides, insulin, homoeostasis model assessment of IR, insulin sensitivity, visceral adiposity index) in patients with prolactinoma, regardless of the degree of decrease in PRL concentrations.^{26,27} Effects on cortisol also cannot be excluded. In dogs with PDH, cabergoline reduces ACTH concentrations, and subsequently cortisol concentrations also decrease.¹⁵ These hypotheses were not evaluated in the cats in the present report.

Conclusions

This is the first report of diabetic remission in cats with hypersomatotropism treated with cabergoline. Further work should be aimed at treating a greater number of animals, best dosage regimens and clarifying cabergoline's mechanism of action. Cabergoline is relatively inexpensive and easy to administer, and should therefore be considered as a possible alternative treatment option, alongside other medical options such as pasireotide, radiotherapy or the definitive treatment option – hypophysectomy. As IGF-1 concentrations do not normalize, cats receiving treatment are likely still under threat from the sequelae of GH excess.

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

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognized high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed

consent (verbal or written) for their use in the publication was obtained from the people involved.

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