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Efficacy of hypophysectomy for the treatment of hypersomatotropism-induced diabetes mellitus in 68 cats

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Abstract

Background: Hypersomatotropism (HST) is an increasingly recognized endocrinopathy in cats and is mostly described associated with diabetes mellitus (DM).

Objectives: To evaluate the efficacy and safety of transsphenoidal hypophysectomy in treating HST and DM in cats.

Animals: Sixty-eight client-owned cats with HST and DM treated by transsphenoidal hypophysectomy.

Methods: Retrospective cohort study. Medical records were reviewed for glycemic control and serum insulin-like growth factor-1 (IGF-1) concentrations. Postoperative complications, death within 4 weeks, and proportion achieving diabetic remission were recorded. Survival times and DM-free intervals were calculated.

Results: Fifty-eight cats (85.3%) were alive 4 weeks postoperatively with 10 (15%) postoperative deaths. Complications included hypoglycemia (n = 9), electrolyte imbalance (n = 9), and transient congestive heart failure (n = 5). Fifty-five cats (95% of 58 surviving cats [81% of all cats undergoing surgery]) had improved control of diabetes. Diabetic remission occurred in 41 cats (71% of 58 surviving cats [60% of all cats]) with insulin administration discontinued after a median of 9 days (range, 2-120). Postoperative 4-week serum IGF-1 concentration nadir was significantly lower in cats achieving diabetic remission (median 20 ng/mL [15-708] than those that did not (324 ng/mL [15-1955]; $P = .03$). All cats received long-term levothyroxine and hydrocortisone PO, alongside desmopressin (conjunctival) in 38 of 53 cats (72%). Recurrence of DM occurred in 5 of 41 cats (12%) after a median of 248 days (range, 84-1232). Median survival time of all cats was 853 days (range, 1-1740).

Conclusions and Clinical Importance: Transsphenoidal hypophysectomy is an effective treatment for cats with HST and DM, with a long-term outcome that compares favorably to existing options.

Abbreviations: CI, confidence interval; CT, computed tomography; DM, diabetes mellitus; GH, growth hormone; HST, hypersomatotropism; IGF-1, insulin-like growth factor-1.

KEYWORDS
acromegaly, cat, diabetic, pituitary, remission, transsphenoidal

1 | INTRODUCTION

Hypersomatotropism (HST) is a common cause of diabetes mellitus (DM) in cats, with a prevalence of 17.8% in diabetic cats in Switzerland and the Netherlands and 24.8% in the UK.[1,2] Hypersomatotropism in cats typically occurs because of excessive growth hormone (GH) production by a functional pituitary somatotroph adenoma or hyperplasia.[3,4] Growth hormone has antagonistic effects resulting in insulin resistance of sufficient severity for cats to develop DM.[3] This excess of GH also leads to increased production of insulin-like growth factor-1 (IGF-1), which can cause increased tissue growth.

Without addressing the underlying excessive GH secretion, it is often challenging to achieve improved diabetic control, or prevent the progression of the acromegalic clinical syndrome. Additionally, if left untreated, the pituitary adenoma can cause signs of central nervous system disease. Reported treatment options for cats with HST include medical management,[5,6] linear-accelerator-based modified radiosurgery, hypofractionated radiation therapy, and stereotactic radiation therapy,[7-9] a single report of cryohypophysectomy[10] and surgical treatment by transsphenoidal hypophysectomy.[11-13]

A recent consensus statement on the treatment of acromegaly in humans recommended transsphenoidal surgery as the primary treatment in most patients, with adjunctive medical management if there is persistent disease after surgery or radiation.[14] In veterinary medicine, the only drugs that improve diabetic control in a small number of cats with HST are the somatostatin analogue, pasireotide, and the dopamine agonist, cabergoline.[5,6,15] Diabetic remission was seen in 3 out of 8 cats treated with long-acting pasireotide, with only mild adverse effects.[5] However, cost remains an important factor limiting the use of this treatment. Although conventional radiation therapy might be effective at reducing the size of pituitary masses, it is associated with a more variable and unpredictable endocrine response in cats with HST.[7,8] Stereotactic radiation therapy for the treatment of 53 cats with HST and DM achieved reduced insulin requirements in 39 (95%) and diabetic remission in 13 (32%) of 41 cats.[9] Even if glycemic control improves, serum IGF-1 does not reduce significantly with hypofractionated radiotherapy regardless of changes in glycemic control,[8,16] resulting in progressive acromegalic features.[17] The single study to date on the use of stereotactic radiation therapy on cats with HST and DM did not report serum IGF-1 concentrations after treatment.[10]

In veterinary medicine, transsphenoidal hypophysectomy was first reported for the treatment of a cat with HST and DM in 2010, with a successful outcome and diabetic remission achieved.[11] The primary aim of this study was to report the long-term efficacy and safety of transsphenoidal hypophysectomy as a treatment for diabetic cats with HST. A secondary objective was to investigate any associations between clinical variables before and after surgery and outcome, as potential prognostic indicators.

2 | MATERIALS AND METHODS

2.1 | Animals

This was a retrospective cohort study, approved by the institutional Ethical Review Board (URN SR2018-1666). All cats that underwent transsphenoidal hypophysectomy for treatment of HST through the Diabetic Remission Clinic of the Royal Veterinary College (London, UK) between April 2012 and April 2018 were included. Cat descriptive data were recorded for all cats (breed, age, sex and neuter status, body weight), and any relevant comorbidities.

2.2 | Diagnosis

Date of original DM diagnosis, preoperative insulin type and dose, serum fructosamine concentration and serum IGF-1 concentration was recorded from clinical records. All cats had a diagnosis of HST based on a diagnosis of DM (consistent with the internationally agreed European Society of Veterinary Endocrinology [ESVE] ALIVE definition of DM - www.esve.org) and serum IGF-1 concentration of >1000 ng/mL. This IGF-1 cutoff is associated with a positive predictive value of 95% for the diagnosis of HST.[1] Serum IGF-1 concentration was measured with a commercially available radioimmunoassay (IGF-1 RIA-CT, Mediagnost, Germany) previously validated in cats.[1,18,19] As the lower and upper limits of IGF-1 quantification of this test are 15 and 2000 ng/mL, values below this range were recorded as 15 ng/mL and those greater than 2000 were recorded as 2000 ng/mL for statistical analysis. All cats underwent full physical examination, complete blood count, serum biochemistry, and urinalysis. Any comorbidities that might increase the risk of general anesthesia or surgery were investigated with surgery performed at the discretion of the supervising clinician and owner. The presence of phenotypic features suggestive of acromegaly (such as prognathism inferior, broadening of the face, enlarged paws) or plantigrade stance consistent with diabetic polyneuropathy was recorded.

All cats underwent contrast-enhanced computed tomography (CT) of the head (Figure 1).[20] Pituitary dorsoventral height was recorded for all cats, with pituitary enlargement defined as a dorsoventral height of >4 mm.[21] Although CT imaging was a requirement for all included cases, pituitary enlargement was not a required diagnostic criterion for HST provided that endocrine testing suggested the presence of HST.[1]

Surgery was performed by 2 surgeons: the first for cases 1 to 41 then the second for cases 42 to 68. Anesthesia, perioperative medications and surgical procedure are outlined in Supplementary Information File 1.

2.3 | Outcome

Postoperative death was recorded as those occurring within 4 weeks of surgery, with the cause of death classified as surgical (procedure related) or medical. Any other postoperative complications sufficient to warrant a change in treatment protocol were recorded from clinical records. Postoperative medical complications, histopathological diagnosis of the excised pituitary tissue, duration of hospitalization, and desmopressin administration were recorded for all cats.

Postoperative serum IGF-1 and fructosamine concentrations, and clinical examination findings (body weight, body condition score), were recorded at 7 days and, where available, 4 weeks. Duration, type, and daily dose of postoperative insulin administration was recorded, with diabetic remission defined according to the ESVE ALIVE definition (www.esve.org) as normoglycemia without insulin or oral antihyperglycemic medications (except low-carbohydrate diets) for at least 4 weeks. For surviving cats that did not achieve diabetic remission, dose and type of daily insulin at the last point of follow-up were recorded. All surviving cats had at least 6 months long-term follow-up, with any cases of recurrence of DM or HST after initial remission (as defined above) recorded. In cats that died or were euthanized, the date and cause of death were recorded as well as DM status where available.

2.4 | Statistical analysis

Descriptive results are reported as mean (±SD) for normally distributed data and median (range) for nonnormally distributed data. Statistical significance was established as $P < .05$. Survival times and DM-free fractions (DM remission defined as above) were estimated using the Kaplan-Meier estimate. Survival analyses were performed both with censoring of cats that subsequently died later than 4 weeks postoperatively for causes suspected to be unrelated to HST or DM,

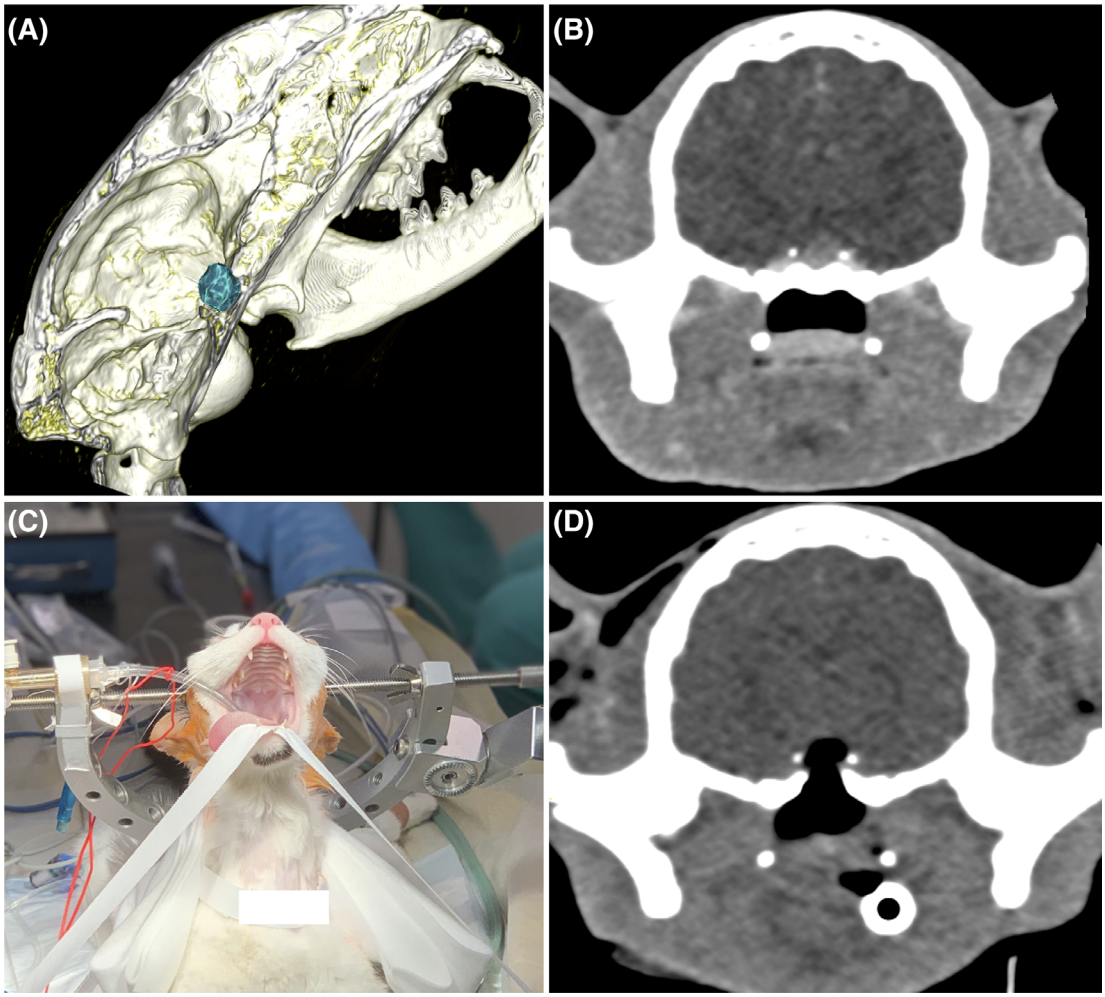

FIGURE 1 A 3-dimensional reconstruction of a computed tomography (CT) scan of the skull of a cat with hypersomatotropism and diabetes mellitus used for surgical planning (A). The pituitary mass is highlighted as a 3-dimensional model computed from freehand region of interest traces on the 2-dimensional CT images. Positioning of a cat in the surgical headframe is also shown (C). A postcontrast transverse CT image (soft tissue window) of the same cat is shown both preoperatively (B) and postoperatively (D), demonstrating removal of the mass with the pituitary fossa now filled with air and a defect in the basisphenoid bone present (D)

and separately with all causes of death included as endpoints. Kaplan-Meier survival analysis was used to compare survival times and DM-free fraction rates among cats with a 4-week postoperative serum IGF-1 concentration nadir of <300 or >300 ng/mL using the log-rank test, with Cox proportion hazard regression used to evaluate any association between pituitary height and survival time or DM-free fraction. Continuous variables (age, body weight, time since DM diagnosis, pituitary mass height, pre- and postoperative serum IGF-1 concentration, preoperative serum fructosamine concentration) were compared between cats that achieved diabetic remission and those that did not using Mann-Whitney *U* tests and independent samples *t* tests. Receiver operator characteristic analysis was performed to evaluate postoperative serum IGF-1 concentration as a predictor of DM remission. Paired patient variables (pre- and postoperative fructosamine, serum IGF-1 concentration, and insulin dose) were compared using paired *t* tests and Wilcoxon signed-rank tests. One-way analysis of variance with post hoc Tukey multiple comparisons tests were used to compare body weights of cats at postoperative reexaminations. The frequency of diabetic remission between breeds, sexes, insulin type, and histologic diagnosis was analyzed using Chi-square test. All data analysis was performed using commercially available statistical software programs (SPSS v22, IBM SPSS Inc, Chicago, Illinois; GraphPad Prism v7.0d, GraphPad Software, La Jolla, California).

3 | RESULTS

3.1 | Animals

Descriptive data regarding signalment and clinical characteristics of 68 cats that underwent transsphenoidal hypophysectomy to treat HST and DM are detailed in Table 1.

TABLE 1 Signalment, clinical, and surgical characteristics of 68 cats undergoing hypophysectomy for treatment of hypersomatotropism-induced diabetes mellitus

	N (%)	Mean ± SD	Median (min-max)
Breed			
Domestic short-haired	47 (69%)		
Domestic long-haired	9 (13%)		
British short-haired	5 (7%)		
Mixed breed	3 (4%)		
Bengal	2 (3%)		
Siamese	1 (2%)		
Maine Coon	1 (2%)		
Sex			
Male neutered	53 (78%)		
Female neutered	15 (22%)		
Age (years)		10.2 ± 2.7	
Body weight (kg)		5.5 ± 1.1	
Phenotypic features of acromegaly	33 (49%)		
Plantigrade stance	10 (15%)		
Days between diagnosis of DM and surgery			170 (46-1419)
Insulin type received at time of surgery			
Porcine lente	27 (40%)		
Protamine zinc	25 (37%)		
Glargine	15 (22%)		
Insulin dose received at time of surgery (U/kg/day)			2.3 (0.6-23.5)
Serum IGF-1 concentration prior to surgery (ng/mL)	1829 (1158-2000)		
Serum fructosamine concentration prior to surgery (μmol/L)		558.7 ± 107.9	
Pituitary height (mm)			6.0 (4.0-14.0)
Surgical duration (hours)		2.5 ± 0.5	
Total theater time including surgical preparation and head frame placement (hours)		3.8 ± 0.5	

Abbreviations: DM, diabetes mellitus; IGF-1, insulin-like growth factor-1.

3.2 | Histopathology

A pituitary adenoma was identified in 52 (76.5%) cats, acidophil hyperplasia in 11 (16.2%) cats, and nondiagnostic pituitary tissue in 5 (7.4%) cats. None of the 5 cats in which the pituitary tissue did not confirm the type of disease died within 4 weeks, with 4 of 5 achieving long-term diabetic remission and improved diabetic control in the remaining cat.

3.3 | Postoperative death and complications

Ten cats (15%) died within 4 weeks of surgery, including 3 (4%) classified as postoperative surgical death without recovering from anesthesia. Postmortem imaging (n = 1) and postmortem examinations (n = 2) of these 3 cats were consistent with mixed ischemic/hemorrhagic cerebrovascular accidents. The sizes of the pituitary masses in these cats were 5.5, 7.0, and 10.0 mm. The causes of death of the other 7 cats (10%) that died after recovery from anesthesia but within the 4-week postoperative period were suspected bacterial meningoencephalitis (n = 5), postoperative hemorrhage (n = 1), and severe hypoglycaemia without a confirmed underlying cause (n = 1). Postmortem examination in 3 of the 5 cats with suspected bacterial meningoencephalitis revealed: diffuse lymphoplasmacytic meningoencephalitis (n = 1), focal lymphoplasmacytic encephalitis with suppurative pharyngitis (n = 1), and diffuse lymphoplasmacytic meningoencephalitis with suppurative inflammation of the pituitary fossa (positive culture of *Escherichia coli* and *Staphylococcus pseudintermedius*) (n = 1). In the latter cat, cerebrospinal fluid analysis revealed a marked neutrophilic pleocytosis 9 days postsurgery (total nucleated cell count = 228 cells/mL, total protein = .62 g/L). Meningoencephalitis was suspected in another 2 cats based on progressive neurological dysfunction and pyrexia within 4 weeks of surgery. Postmortem examination in 1 cat revealed a large volume of hemorrhage in the region of the pituitary fossa as well as evidence of increased intracranial pressure and foramen magnum herniation of the cerebellum. Although antemortem CT imaging performed by the primary care practice in the cat that was euthanized because of severe hypoglycaemia was suggestive for a mass associated with the pancreas, postmortem examination was not available to confirm this.

Further postoperative complications are listed in Table 2. Transient congestive heart failure occurred after surgery in 5 cats and was presumed to be secondary to volume overload, with only 1 of these occurring in the 57 cases (2%) after a reduction in rate of fluid administration after surgery was instituted. In 4 of the 9 cats experiencing postoperative hypoglycemia, this occurred during tapering of exogenous insulin dosage, whereas 5 occurred after insulin therapy had been discontinued. The hypoglycemia was suspected to be related to sepsis in 4 of the 9 cats and all of these were subsequently euthanized within 4 weeks of surgery as a result of a failure to improve, whereas in another 4 cats the hypoglycemic episode resolved or responded to treatment. Hypoglycemia unresponsive to treatment occurred in 1 of the 9 cats, which was subsequently euthanized 17 days after surgery.

3.4 | Outcome

Outcome data, including the diabetic remission rate, are summarized in Table 3. Of the 14 cats achieving improved glycemic control but not diabetic remission, there was a significant reduction in median total daily insulin dose from 2.3 U/kg/d (range, 0.6-23.5) preoperatively, to 0.5 U/kg/d 4 weeks postoperatively (range, 0.1-2.9; $P < .001$). Among surviving cats, postoperative serum fructosamine concentration also significantly reduced from 558.7 (±107.9) to 304.0 μmol/L (±134.3; $P < .001$). Of the 3 cats which had no improvement in diabetic control, 2 were the first cats operated on by each surgeon.

Tests for associations between recorded preoperative clinical variables and outcome of diabetic remission did not reveal any statistically significant associations (Table 4). There was no significant difference in surgery duration between cats that achieved diabetic remission (mean 2.5 hours ± 0.5) and those that did not (mean 2.7 hours ± 0.5; $P = .27$). There was also no significant difference of surgery duration between cats that died because of suspected or confirmed postoperative meningoencephalitis or sepsis (mean 2.2 hours ± 0.4) and those that did not (mean 2.6 hours ± 0.5; $P = .08$). No significant difference was found in pituitary height

TABLE 2 Postoperative complications for 65 cats undergoing hypophysectomy for treatment of hypersomatotropism-induced diabetes mellitus that recovered from surgery

	N (%)	Median (min-max)
Postoperative electrolyte change requiring variation from treatment protocol		
Hypernatremia	6 (8%)	
Hypokalemia	3 (5%)	
Transient congestive heart failure	5 (7%)	
Hypoglycaemia[a]	9 (14%)	
Time from surgery to hypoglycemia (days)		16 (10-168)
Transient postoperative neurological signs		
Unilateral orbicularis oculi paresis	4 (6%)	
Vestibular ataxia	2 (3%)	
Seizures	2 (3%)	
Reduced tear production	2 (3%)	
Right-sided oculomotor neuropathy + right-sided compulsive circling	1 (2%)	
Postoperative pyrexia	6 (9%)	
Soft palate wound breakdown	0 (0%)	
Postoperative death within 4 weeks		
Overall	10 (15%)	
Nonrecovery from anesthesia	3 (4%)	
Dead within 4 weeks after recovery from anesthetic	7 (10%)	

[a]Blood glucose <3.3 mmol/L according to the ALIVE definition.

between cats that died because of suspected or confirmed postoperative meningoencephalitis or sepsis (median 5.3 mm; range, 4.0-7.0) and those that did not (median 6.0 mm; range, 4.0-14.0; $P = .29$).

Seven-day and 4-week postoperative serum IGF-1 concentration was available in 44 and 43 cats, respectively. The median preoperative serum IGF-1 was 1829 ng/mL (1158-2000), median 7-day IGF-1 was 133 ng/mL (range, 15-2000: $P < .001$), and median 4-week IGF-1 was 28 ng/mL (range, 15-1955; $P < .001$) (Figure 2). Overall, of 55 cats for which serum IGF-1 concentration was available at 7 days and/or 4 weeks postoperatively, 44 (80%) experienced a reduction of serum IGF-1 concentration to <300 ng/mL within 4 weeks of surgery. Postoperative 4-week serum IGF-1 nadir was significantly lower in cats that went into diabetic remission (median 20 ng/mL; range, 15-708) than cats that did not (median 324 ng/mL; range, 15-1955; $P = .03$). Of the cats that achieved improved glycemic control but not diabetic remission for which postoperative serum IGF-1 concentrations were available (n = 9), median postoperative 4-week serum IGF-1 nadir was 132 ng/mL (range, 15-910). The 3 cats that experienced no improvement in glycemic control all had persistently increased serum IGF-1 concentrations 4-weeks postoperatively (1955, 1651, and 1975 ng/mL, respectively) and 2 were the first cats operated on by the

TABLE 4 Results of bivariate tests for association between patient variables and outcome of diabetic remission (yes or no) in 68 cats with hypersomatotropism and diabetes mellitus undergoing transsphenoidal hypophysectomy

Variable	*P*-value	Test
Age	.91	*t* test
Body weight	.98	*t* test
Breed	.81	Chi-square
Sex	.87	Chi-square
Duration since diabetes mellitus diagnosis	.20	Mann-Whitney *U* test
Maximum pituitary height (mm)	.73	Mann-Whitney *U* test
Preoperative serum IGF-1 concentration	.85	Mann-Whitney *U* test
Preoperative serum fructosamine concentration	.65	*t* test
Preoperative insulin dose (U/kg/d)	.09	Mann-Whitney *U* test
Insulin type	.6	Chi-square

Abbreviation: IGF-1, insulin-like growth factor-1.

TABLE 3 Outcome for 68 cats undergoing hypophysectomy for treatment of hypersomatotropism-induced diabetes mellitus

	N (%)	Median (min-max)	Mean ± SD
Duration of hospitalization (days)			
Overall		9 (4-21)	
Cases 1-34		10 (4-21)*	
Cases 34-68		7 (5-14)*	
Postoperative glycemic control			
Improved	55 (81%)		
	(95% of 58 survivors)		
No improvement	3 (4%)		
	(5% of 58 survivors)		
Diabetic remission	41 (60%)		
	(71% of 58 survivors)		
Duration of postoperative insulin therapy for those achieving remission (days)		9 (2-120)	
Recurrence of diabetes mellitus	5 (12%)		
Time from remission to recurrence (days)		248 (84-1232)	
Postoperative body weight (kg)			
4 weeks (N = 26)			5.1 ± 1.0**
3 months (N = 31)			5.7 ± 1.2
12 months (N = 15)			6.3 ± 1.3**
Postoperative conjunctival desmopressin (N = 53)			
Discontinued postoperatively	15 (28%)		
Duration of treatment for those discontinued (days)		60 (28-180)	
Treatment ongoing at last follow-up	38 (72%)		

*$P < .001$; **$P = .007$.

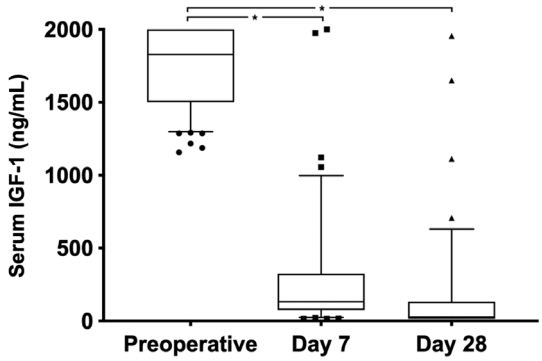

FIGURE 2 Box and whisker plots demonstrating serum insulin-like growth factor-1 (IGF-1) concentrations of cats undergoing transsphenoidal hypophysectomy for treatment of hypersomatotropism and diabetes mellitus preoperatively (n = 68), 7 days postoperatively (n = 43), and 28 days postoperatively (n = 43). Box represents interquartile range and whiskers represent 10th to 90th percentiles with central line representing the median. Solid circles, squares, and triangles represent cases below the 10th or above the 90th percentiles. *Statistically significant difference ($P < .05$)

2 surgeons. Receiver operator characteristic analysis showed that a cutoff serum IGF-1 nadir concentration of >344 ng/mL in the first 4 weeks was 90% specific (95% confidence interval [CI] 76.3%-97.2%) for predicting failure to achieve DM remission but 50% sensitive (95% CI 21.1%-78.9%). Eight cats died before postoperative serum IGF-1 concentration was measured and postoperative serum IGF-1 data were missing from patient records for 7 cats. Median 4-week serum IGF-1 nadir was significantly higher in the first 3 cats operated on by each surgeon (median 813 ng/mL; range, 308-1975) compared to the subsequent cats (median 43 ng/mL; range, 15-1955; $P < .001$). Of these 6 cats, all survived the 4-week postoperative period but only 2 (33%) went into diabetic remission postoperatively compared to 39 (75%) of the remaining 52 cats ($P = .03$). There was no significant difference in the number of cats achieving diabetic remission ($P = .88$) or postoperative death ($P = .98$) between surgeons.

3.5 | Long-term follow-up

When considering all causes of death as endpoints, 1-, 2-, 3-, and 4-year estimated survival rate was respectively 77.3% (95% CI 65.1%-85.7%), 56.9% (95% CI 42.0%-66.3%), 37.4% (95% CI 21.1%-53.6%), and 31.2% (95% CI 14.9%-49.1%). The overall median survival time including all causes of death was 853 days (28 months; 95% CI 478-1228 days; Figure 3A). Twenty cats (29.4%) survived the 4-week postoperative period and subsequently died or were euthanized for causes suspected to be unrelated to HST or DM. One-, 2-, 3-, and 4-year estimated survival rate with only HST or DM-related death as endpoints was 84.8% (95% CI 73.5%-91.5%), 84.8% (95% CI 73.5%-91.5%), 84.8% (95% CI 73.5%-91.5%), and 70.7% (95% CI 36.3%-88.8%, respectively (Figure 3B).

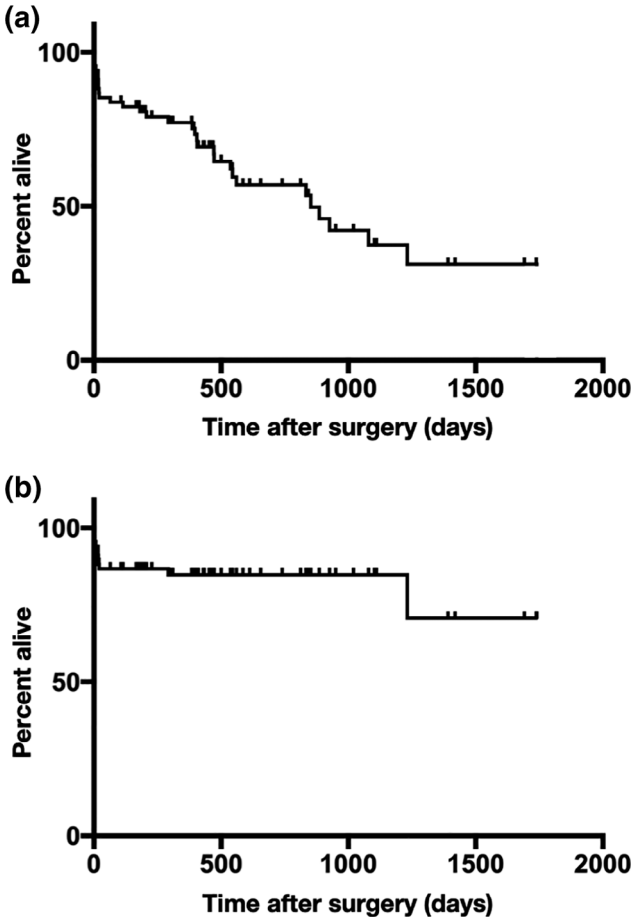

FIGURE 3 A, Estimated survival curve for 68 cats with hypersomatotropism (HST) and diabetes mellitus (DM) that underwent transsphenoidal hypophysectomy, including all causes of death as end points. Only cats that were alive at the last point of follow-up were censored for this analysis (vertical bars). B, An estimated survival curve for the same 68 cats, with those that were alive at the last point of follow-up or that died for causes suspected to be unrelated to HST or DM censored (vertical bars)

There was recurrence of DM in 5 cats (12%), with estimated 1-, 2-, and 3-year DM-free fractions of 91.6% (95% CI 76.1%-97.2%), 91.6% (95% CI 76.1%-97.2%), and 78.5% (95% CI 40.6%-93.2%). Of the 5 cats experiencing a recurrence of DM, serum IGF-1 concentration at the time of recurrence was available for 2 cats (1686 and 102 ng/mL, respectively). Repeat intracranial imaging was not available for these cats. Three cats responded well to reintroduction of insulin, whereas the cat with serum IGF-1 concentration of 1686 ng/mL achieved another DM remission after treatment with pasireotide and 1 cat was euthanized. One cat that experienced a reduction in insulin requirement postoperatively without entering diabetic remission, also suffered a deterioration in glycemic control after 586 days with a concurrent increase in serum IGF-1 concentration to 918 ng/mL, from 132 ng/mL 4 weeks postoperatively. This cat underwent repeat CT imaging at this time with no recurrence of the previous pituitary mass identified and responded to an increased insulin dose. Neither pituitary height (hazard ratio 0.915, $P = .91$) or 4-week

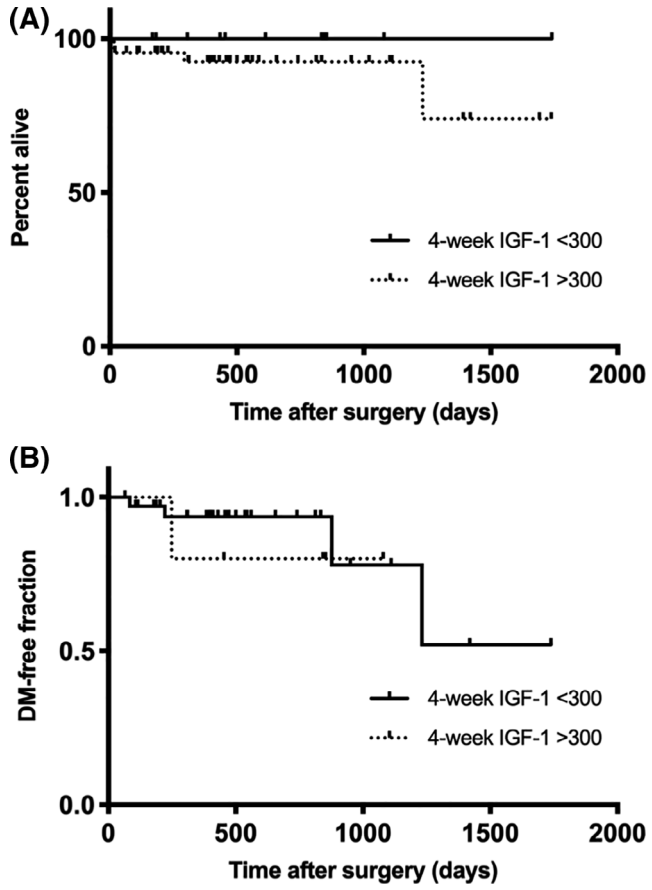

FIGURE 4 A, Comparison of estimated survival curves for all 68 cats that underwent transsphenoidal hypophysectomy for treatment of hypersomatotropism (HST) and diabetes mellitus (DM) with a 4-week postoperative serum insulin-like growth factor-1 (IGF-1) concentration nadir of <300 ng/mL or >300 ng/mL (P = .37, log rank test). B, Comparison of DM relapse-free fraction curve for 41 cats that entered diabetic remission after transsphenoidal hypophysectomy for treatment of HST and DM between cats with a 4-week postoperative serum IGF-1 concentration nadir of <300 or >300 ng/mL (P = .45, log rank test)

postoperative serum IGF-1 concentration (hazard ratio 0.983, P = .48) was associated with survival. These variables were also not associated with DM-free fraction (pituitary height hazard ratio 0.407, P = .57; 4-week postoperative serum IGF-1 concentration hazard ratio 0.984, P = .37). Survival and DM-free fraction curves were also compared for cats with a 4-week postoperative serum IGF-1 concentration nadir of <300 or >300 ng/mL, with no significant difference identified (Figure 4).

4 | DISCUSSION

The results of this study demonstrate that transsphenoidal hypophysectomy is an effective treatment for cats with HST and DM. The rate of diabetic remission achieved exceeds previously reported outcomes after medical management or radiation therapy for treatment of HST in cats.[5,8,9] There was a rapid reduction in insulin requirements, a higher rate of normalization of serum IGF-1 concentrations and a low rate of recurrence. Overall median survival time was 853 days.

Postoperative death rate (15%) was consistent with previous literature describing pituitary surgery in dogs and cats,[22-24] with perioperative complications rare and typically treatable. Although the largest previously reported cohort of cats undergoing hypophysectomy found a death rate of 2 out of 7 cats treated for pituitary-dependent hyperadrenocorticism, comparisons with this study are limited by the small number of cats and different disease process being treated. Recent studies into hypophysectomy for the treatment of pituitary-dependent hyperadrenocorticism in dogs in 1 center have reported death rates of 8% to 9%.[23-25] However, assessment of the initial death rate of 19.2% in the first 26 dogs in 1 center[23] was the same as the death rate recently reported by another center (19.2%) following hypophysectomy in 26 dogs.[26] Although it is challenging to compare death rates among species, centers, and indications for surgery, the postoperative death rate (14.7%) in our cohort of cats treated at a single center is as expected and in the same range as reported death rates for hypophysectomy at different institutions.

Although radiation therapy has demonstrated the ability to reduce the size of pituitary adenomas, studies have demonstrated variable diabetic remission rates when treated with conventional radiation therapy.[7,8,27] The diabetic remission rate of 70.7% of survivors (60.3% when accounting for 4-week postoperative deaths) after hypophysectomy in the current study is greater than the 32% (13 of 41 cats) treated with stereotactic radiation therapy.[9] In the case series of cats treated with stereotactic radiation therapy, 95% of cats (39 out of 41) had reduced insulin demands.[10] Although we have found diabetic remission can be achieved through treatment with pasireotide, diabetic remission using long-acting pasireotide was achieved in only 3 out of 8 cats.[5] Although serum IGF-1 concentration significantly reduced after treatment with pasireotide, IGF-1 did not consistently normalize, nor did tumor size significantly reduce. There also remain important lifelong cost and availability limitations to medical treatment, making this option rarely feasible in clinical practice currently.[3,5,6] The increased rate of resolution of both HST and DM compared to other available treatment options supports the suggestion that transsphenoidal hypophysectomy should be considered the most ideal treatment when aiming for remission of HST and DM in cats.

Time to remission of DM after hypophysectomy in cats was rapid and consistent, occurring after a median of 9 days. This early onset of improvement in glycemic control after hypophysectomy is markedly different to reported treatments. Diabetic remission after radiation therapy in cats with HST typically has been variable in onset, ranging from weeks to several years, with a median of 17 weeks to 3.6 months.[8,27] There are fewer data available regarding medical treatment and although short-acting pasireotide increases insulin sensitivity within 5 days,[6] using a long-acting formulation allowed cessation of insulin administration after 89 and 91 days in 2 cats that achieved diabetic remission.[5] It is likely that the immediate removal of the pituitary gland at surgery leads to a more rapid reduction in circulating GH, causing a more rapid increase in insulin sensitivity.

Long-term follow-up demonstrated sustained DM remission in the majority of cats that achieved diabetic remission, with recurrence of DM seen in only 5 cats (12%) and a 3-year estimated DM-free fraction of 79%. These findings are in contrast to the variable long-term outcome with radiation therapy for treatment of HST and DM in cats, with recurrence of DM within 2 years of hypofractionated radiation therapy in 3 out of 6 cats that initially achieve diabetic remission.[8] Stereotactic radiation therapy is associated with recurrence of DM in 38% of 13 cats that initially achieved remission.[9] Our results revealed a median survival time of 853 days when including all causes of death. This compares favorably to some reports of radiation therapy for treatment of HST and DM in cats, with an estimated 2-year survival rate of 50% in 1 study using hypofractionated radiation therapy,[27] as well as median survival times of 840 days (hypofractionated radiation therapy)[8] and 522 days (conventional fractionated radiation therapy).[28] The median survival time we report here of 853 days (95% CI 478-1228 days) is shorter than, although falling within the 95% CIs, the median survival time of the single SRT study reported to date of 1072 days (95% CI 845-1339 days).[10] Accounting for the learning curve we describe here as a de novo hypophysectomy program, we might anticipate that survival times will improve with greater surgeon and team experience. There is limited data regarding long-term outcome and recurrence rates after medical treatment of HST and although none of 3 cats that achieved diabetic remission after treatment with pasireotide had a recurrence of DM, follow-up in this trial was limited to 6 months.[5]

There was a consistent and marked reduction in serum IGF-1 concentration after hypophysectomy in the current study. Normalization of serum IGF-1 concentration to <300 ng/mL within 4 weeks of surgery occurred in 44 of 55 cats (80.0%), in contrast to variable serum GH and IGF-1 concentration reductions after radiation therapy.[8,16,18] Normalization of IGF-1 is an important biomarker for identifying those who have achieved normalization of endogenous GH. This is an important goal of therapy as persistently excessive endogenous GH would have continued disease effects even if good glycemic control is achieved.[17] The current study demonstrates that surgical removal of the pituitary gland is an effective treatment to induce a rapid and consistent reduction of circulating IGF-1.

Of the 17 (29%) cats surviving the 4-week postoperative period that did not enter diabetic remission, 14 had a significant reduction in insulin requirement and serum fructosamine concentration postoperatively, indicative of a partial treatment response. The median 4-week postoperative serum IGF-1 nadir concentration among these cats was 132 ng/mL (range, 15-910), reflecting a normalization of serum IGF-1 in most of these cases. This is similar to previous findings with radiation therapy and medical management with pasireotide where cats that do not respond completely might still achieve improved glycemic control.[5,8,9] In addition, the 3 cats that experienced no improvement in glycemic control all had persistently increased serum IGF-1 concentrations, suggesting that monitoring serum IGF-1 concentration for evidence of ongoing HST postoperatively might be a useful method of detecting cases of incomplete mass removal at surgery, and hence increased likelihood of continued DM and insulin resistance. Lack of diabetic remission could be caused by several factors including microscopic remnant of neoplastic somatotrophs, permanent beta-cell damage, beta-cell exhaustion, or underlying type 2 DM.

Of the 10 cats (15%) that died within 4 weeks of surgery, the majority of these occurred after initial recovery from the procedure, with bacterial meningoencephalitis the most frequently identified cause. Postoperative meningoencephalitis has not been identified as a risk in previous reports of transsphenoidal hypophysectomy in dogs or cats.[22,25,26] It could be expected that this would be a risk, given the proximity to the nasopharyngeal flora and resulting nonsterile nature of areas of the surgical site. Comparison with previous findings in dogs should be treated with caution due anatomical differences and low number of cats with which to compare directly.[22] Meningoencephalitis was only confirmed on postmortem examination in 3 cats, whereas there was a clinical suspicion for cause of death in a further 2 cats. Nevertheless, these findings in combination with a suspicion of sepsis in 4 cats with hypoglycaemia suggest that postoperative meningoencephalitis is a risk after this procedure and supports the use of peri- and postoperative broad-spectrum antibiotics, and careful monitoring for signs of pyrexia in the first 4 weeks after surgery.

Three cats (4%) died without recovering from general anesthesia, with each of these having evidence of major ischemic and hemorrhagic cerebrovascular accidents. This is consistent with the anticipated risks of surgical access to the pituitary fossa, because of the anatomical relationship to the cerebral arterial circle and the potential consequences of surgical damage to this area. Interestingly, postoperative medical complications such as serum electrolyte abnormalities were rare, likely because of regular monitoring of hydration status and encouragement of early water intake. In a previous study describing hypophysectomy for the treatment of pituitary-dependent hyperadrenocorticism in 7 cats, it was suggested that less marked changes in plasma sodium concentrations were seen compared to dogs undergoing the same procedure.[22] Similarly, although 5 cats (7%) developed transient congestive heart failure secondary to volume overload, only 1 occurred in the 57 cases after a reduction in the rate of fluid administration after surgery was instituted. Although transient mild neurological complications were seen in 8 surviving cats, permanent neurological deficits were not documented.

Although postoperative hypoglycemia was encountered in 9 cats after a median of 16 days, there was a clinical suspicion of sepsis as the underlying cause in 4 of these cats, which were subsequently euthanized. In the 5 cats where hypoglycaemia occurred after discontinuation of exogenous insulin, it is possible that this was associated with a sudden resumption of insulin sensitivity, increased endogenous insulin production, or both. It is also possible that an unidentified subclinical hypoglycaemia occurs during this time period in many cases.

There was evidence of some cats gaining body weight postoperatively, particularly 1-year postoperative weight gain. Lack of GH following hypophysectomy could be associated with the development of obesity, given its marked stimulation of lipolysis and the association between low levels of GH and obesity in humans.[29] Serum ghrelin concentration increases after radiotherapy for treatment of HST in cats,[30] but any association with weight gain requires further investigation. All cats received hydrocortisone and levothyroxine

supplementation with thyroid and dose monitoring according to serum total thyroxine concentrations performed at their primary care practices, limiting a more specific analysis. Further prospective investigation into weight gain, body condition scores, and appetite postoperatively would be beneficial. It nevertheless seems prudent to monitor body weight postoperatively.

Conjunctival administration of desmopressin was discontinued after a median of 60 days in 15 of 53 cats (28%), with the majority of cats still receiving ongoing conjunctival desmopressin for presumed central diabetes insipidus at long-term follow-up. This is in contrast to previous studies into hypophysectomy in dogs with pituitary-dependent hyperadrenocorticism, whereby only 22% of dogs in the largest case series required desmopressin until final follow-up.[24] Indeed, in the case series of 7 cats with pituitary-dependent hyperadrenocorticism treated by hypophysectomy, no cats required desmopressin for longer than 2 weeks.[22] It is possible that the approach of attending veterinarians to ceasing supplementation in the current cohort was more cautious than in previous reports, leading to its prolonged administration.

Despite the change of surgeon that occurred after 41 cases, outcomes were similar between both study periods. There were smaller decreases in serum IGF-1 concentration seen in the first 3 cases for both surgeons. This might be consistent with the steep learning curve previously reported for transsphenoidal hypophysectomy in both veterinary and human medicine.[23,31] As the second surgeon was instructed in the technique by the first surgeon, the findings of the current study also support the trainability of this procedure between surgeons. However, it is important to note the challenging nature of the procedure limits its current availability, both in terms of the equipment and skillset required to perform the surgery, as well as the intensive perioperative medical management and anesthetic monitoring requirements. Another consideration of note is the median duration of hospitalization of 9 days after hypophysectomy in our study sample. Furthermore, the decision taken to pursue surgical intervention should be made in acknowledgement of the perioperative risks involved, as documented in the current study.

There were 5 cats for which submitted pituitary tissue was nondiagnostic, likely related to the loss of sections of the excised mass into the surgical suction system during removal and the potential for focal or multifocal adenomatous change in the pituitary gland in cats with HST.[4] These 5 cats included the first and third cat operated on, suggesting that surgeon experience might play a role in obtaining a diagnostic sample. This study was limited by the retrospective nature of the data collection, particularly in terms of long-term follow-up such as incomplete recording of serum IGF-1 concentrations and body weight postoperatively. However, the study did benefit from relatively large numbers, as well as a consistent nature of the surgical and postoperative treatment protocol at the study institution.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the Royal Veterinary College Ethical Review Board (URN SR2018-1666).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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