Hypersomatotropism, Acromegaly, and Hyperadrenocorticism and Feline Diabetes Mellitus

Stijn J.M. Niessen, DVM, PhD, PGCVetEd, FHEA, MRCVS[a,b,*],
David B. Church, BVSc, PhD, MACVSc, MRCVS[a],
Yaiza Forcada, DVM, MRCVS[a]

KEYWORDS

• Hypersomatotropism • Hyperadrenocorticism • Diabetes mellitus
• Other specific types of diabetes • Pituitary • Adrenal • Pancreas • Insulin resistance

KEY POINTS

- Diabetes mellitus in cats most commonly results from a primary disease process classified as type 2 diabetes, but in a proportion of cats, it is the consequence of another specific disease and classified as "other specific type of diabetes."
- Hypersomatotropism, which can result in acromegaly, usually results in diabetes classed as "other specific type of diabetes—subclass, endocrinopathies." It has been reported to be a primary cause of feline diabetes in up to one-third of insulin-treated diabetic cats presented for assessment of glycemic control in UK primary practices.
- Hyperadrenocorticism-induced diabetes is another example of "other specific type of diabetes" and although seemingly less common, when hyperadrenocorticism occurs, it will cause diabetes in 80% of cases.
- Recognition of these and other specific forms of diabetes, and specifically differentiation from type 2 diabetes, is crucial to enable election of the best possible treatment options and provision of the most accurate prognosis.
- Diagnosis of both feline hypersomatotropism and feline hyperadrenocorticism requires careful consideration of the clinical picture and usually a combination of diagnostic tests.
- Diabetic remission can be achieved when the diabetes is recognized to be a form of an "other specific type of diabetes" associated with insulin resistance, provided it is in an early phase and there is adequate treatment of the underlying etiology.

Funding Sources: The Royal Veterinary College.
Conflict of Interest: Nil.
[a] Department of Veterinary Clinical Sciences, The Royal Veterinary College, University of London, Hawkshead Lane, North Mymms AL9 7TA, Herts, UK; [b] Diabetes Research Group, Institute for Cellular Medicine, Medical School Newcastle, Framlington Place, Newcastle-upon-Tyne, Tyne and Wear NE2 4HH, UK
* Corresponding author. Department of Veterinary Clinical Sciences, Royal Veterinary College, University of London, Hawkshead Lane, North Mymms, Herts AL9 7TA, UK.
E-mail address: sniessen@rvc.ac.uk

Vet Clin Small Anim 43 (2013) 319–350
http://dx.doi.org/10.1016/j.cvsm.2012.12.004 **vetsmall.theclinics.com**
0195-5616/13/$ – see front matter © 2013 Elsevier Inc. All rights reserved.

INTRODUCTION

When confronted with a diabetic cat in clinical practice, it is tempting to assume we are dealing with a cat with a form of diabetes mellitus akin to human type 2 diabetes mellitus. Indeed, most feline cases will have a form of diabetes that occurs during middle or older age, which can be associated with obesity, inactivity, initial endogenous hyperinsulinemia (ultimately usually followed by endogenous hypoinsulinemia), and insulin resistance, as well as islet cell dysfunction and perhaps amyloid deposition[1,2] (see article by Dr Rand, elsewhere in this issue). Additionally, genetic research has provided further evidence toward a shared pathogenesis of feline diabetes and human type 2 diabetes.[3] Therefore, the immediate classification of these cats as having type 2 diabetes is often justified.

Management of diabetic cats can at times prove challenging,[4] however, and in many of these challenging cases, the etiopathogenesis of the diabetes is not type 2, but rather underlying disease processes better categorized as "other specific types of diabetes." Indeed, various other disorders outside the endocrine pancreas could play a crucial role in the etiology of the disease in a significant proportion of cases. Understanding and recognizing that a patient might not have type 2 diabetes will affect optimal management options and prognosis of the patient in question. This article, therefore, deals with other specific types of diabetes—subclass endocrinopathies in cats, and, more specifically, diabetes induced by excess growth hormone (ie, hypersomatotropism resulting in acromegaly) and cortisol (hyperadrenocorticism).

HYPERSOMATOTROPISM AND ACROMEGALY

Hypersomatotropism (HS) implies a state of production of excess growth hormone, whereas acromegaly is the name of the syndrome that results from that state of excess growth hormone production. Hypersomatotropism might therefore result in acromegaly, although all signs constituting the syndrome of acromegaly might not always be present with hypersomatotropism, especially early on in this slowly progressive disease process. A growth hormone–induced postreceptor defect in insulin action at the level of target tissues is thought to explain why most cats with acromegaly have concurrent diabetes mellitus.[5] The past 6 years have seen a renewed interest in the potential for excess growth hormone to induce and complicate diabetes in the cat. In fact, feline hypersomatotropism is now being recognized as an important cause of feline diabetes, largely as a result of 3 studies. All studies suggested that feline acromegaly occurs in a significant proportion of diabetic cats, especially those with insulin resistance. Estimates of prevalence in the diabetic cat population from 2 studies range from 1 in 3 to 1 in 4[5–7]; however, the method of sample recruitment could have influenced the results of these studies (for details please refer to section on hypersomatotropism prevalence that follows). Nevertheless, even when adhering to a more conservative estimate, this has quite clearly justified the initiation of several studies on various aspects of this endocrinopathy, including more careful evaluation of etiology, clinical presentation, and management aspects.

PREVALENCE OF HYPERSOMATOTROPISM

A screening study in which veterinarians in primary practice were offered free fructosamine measurements in diabetic cats, regardless of level of glycemic control, revealed that 59 (32%) of 184 diabetic cats had insulinlike growth factor-1 (IGF-1; see hypersomatotropism diagnostics section later in this article) concentrations strongly suggestive of acromegaly (>1000 ng/mL).[5] Of these 59 cats, a subpopulation was more

closely evaluated with intracranial contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI), as well as growth hormone (GH) concentration evaluation so as to conclusively establish the diagnosis of hypersomatotropism. The diagnosis was subsequently confirmed in 94% of these more carefully assessed cases, proving the original estimation of prevalence among these cats, made on the basis of raised IGF-1 concentrations only, to be likely close to the prevalence in a similarly selected population. Another study in the United States retrospectively assessed medical records of 74 diabetic cats with an IGF-1 concentration recorded, to determine the specificity and sensitivity of IGF-1 for diagnosis of acromegaly.[8] Of those classed as poorly controlled, 26% had IGF-1 levels consistent with a diagnosis of acromegaly; however, the selection criteria likely overestimated the prevalence among this diabetic cat population, as samples could have been preferentially evaluated for IGF-1 measurement, based on an existing suspicion of acromegaly. In a study of diabetic cats with insulin resistance and poor glycemic control (insulin dose >6 U/cat and mean blood glucose >300 mg/dL), all 16 cats had a pituitary mass on imaging and 12 (75%) were classed as acromegalic based on IGF-1 concentrations or suggestive signs together with normal adrenal function tests.[6] However, the argument of bias applies to a significantly lesser extent to the authors' prevalence studies,[5,7] in which prospectively IGF-1 was determined on serum submitted for fructosamine evaluation. A degree of bias may still persist also with this study type, because fructosamine evaluation might be opted for in light of suboptimal glycemic control, a phenomenon more frequently encountered with feline hypersomatotropism than with uncomplicated type 2 diabetes (the latter group might not even attend a veterinary practice on a regular basis or cease to do so in case of diabetic remission having been achieved). Nevertheless, it could equally be argued that the previously mentioned studies in fact also underestimate the true prevalence of acromegaly, as a rather arbitrary cutoff for IGF-1 was chosen (1000 ng/mL), misclassifying cases with a borderline IGF-1 or an IGF-1 that would have increased following initiation of exogenous insulin therapy (please refer to section on hypersomatotropism diagnostics). Additionally, a proportion of diabetic cats that prove difficult to control might be euthanized on the request of owners and therefore would not benefit from further assessments and inclusion in these screening studies.

In light of these surprising results, a more extensive evaluation of diabetic cats in the United Kingdom was undertaken by the authors' research group, using the same methodology as in the first study, which revealed similarly high prevalence numbers after 4 years of screening of diabetic cats. A total of 1222 diabetic cats had IGF-1 determined and 334 (26.4%) showed an IGF-1 concentration suggestive of hypersomatotropism.[7] All 3 studies highlight the difficulty of establishing unbiased prevalence figures. Nevertheless, the prevalence of hypersomatotropism seems sufficiently high to warrant its consideration when dealing with diabetic cats and particularly when problems with glycemic control arise. In light of the significant impact on prognosis and management, one could even argue that routine screening of diabetic cats for the presence of hypersomatotropism is beneficial, just as we screen for urinary tract infections in diabetics, presence or absence of an adrenal tumor in cases with clinical signs of hyperadrenocorticism, or underlying disease in cases with immune-mediated hemolytic anemia. Given the strong association with poorly controlled diabetes, prompt screening is definitely indicated if cats are not well controlled within 2 to 4 months of institution of therapy, or require a dose of 1.5 IU/kg or more. Early detection could have a beneficial impact on response to treatment, especially if beta cell mass is preserved and remission, therefore, a possibility. If screening is applied, however, the characteristics and dynamics of serum total IGF-1 as a screening tool

should be taken into account (please refer to section on hypersomatotropism diagnostics).

ETIOLOGY OF HYPERSOMATOTROPISM

Traditionally, hypersomatotropism or acromegaly in the cat has been seen as a process caused by excess endogenous growth hormone secretion caused by a pituitary adenoma. A more systematic evaluation of pituitary histopathology in a larger number of patients is currently ongoing and suggests that, alongside a vast majority with indeed an acidophilic adenoma, some cases instead display acidophilic hyperplasia.[5,9] If there are indeed at least 2 underlying etiologic mechanisms, questions arise over a possible interrelationship between them (eg, initial hyperplasia leading to adenomatous change or presence of a suprahypophyseal process or stimulus).[4,5,9,10] In this respect, a comparison to current hypotheses on the etiology of feline hyperthyroidism can be made.

When hypersomatotropism is present, GH hypersecretion results in excess production of IGF-1. The combination of excess circulating GH and IGF-1 will eventually result in the clinical syndrome of acromegaly, which is directly related to the physiologic function of these hormones (**Fig. 1**).

SIGNALMENT AND PRESENTATION OF HYPERSOMATOTROPISM

The basic characteristics of recently reported cats are shown in **Table 1**. Presence of insulin resistant diabetes mellitus has been shown to be a risk factor for presence of hypersomatotropism. Nevertheless, when using a screening approach among diabetic cats, a significant number of detected patients will appear insulin sensitive at

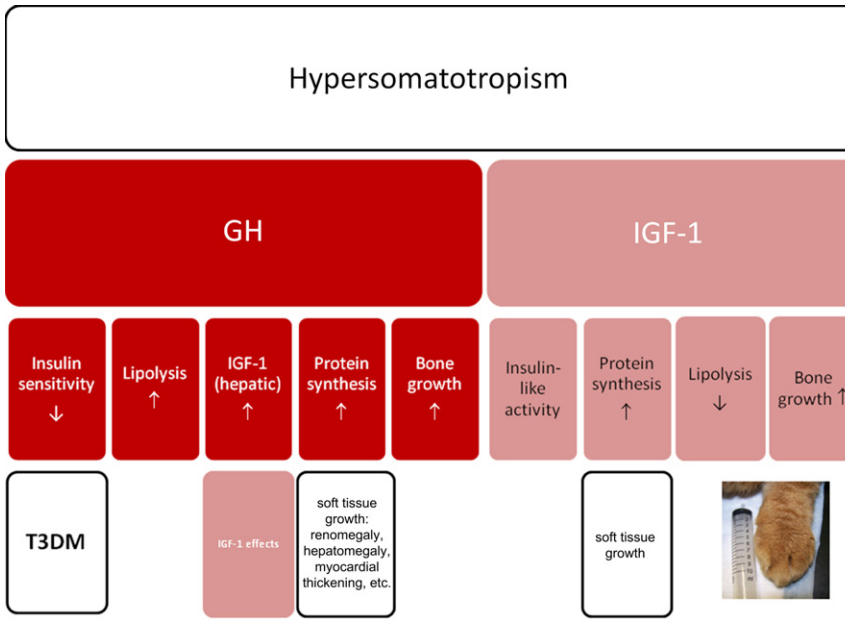


Fig. 1. Overview of pathophysiology of hypersomatotropism. GH, growth hormone; IGF-1, insulin like growth factor 1; T3DM, other specific type of diabetes/type 3 diabetes.

Table 1
Basic characteristics of cats with hypersomatotropism and cats with hyperadrenocorticism

	Hypersomatotropism	Hyperadrenocorticism
Median age, y (range)	11 (4–19)	10 (5–16)
Gender	Male bias	No convincing bias
Breed	Domestic short hair bias	Domestic short hair bias
Weight	Often weight gain (median 5.8 kg, range 3.5–9.2)	Often weight loss
Insulin requirements	Insulin resistance frequent, and ultimately often extreme (median 7 IU twice a day, range 1–35)	Insulin resistance frequent, yet not always and not usually extreme

time of the initial diagnosis. Interestingly, data acquired using that same screening approach suggest that the "typical" acromegalic phenotype is not consistently present, possibly related to the gradual onset of hypersomatotropism-induced changes and/or previous failure to screen assumed "atypical" cases. Interestingly, only 24% of clinicians suspected the presence of hypersomatotropism in diabetic cats found to have an IGF-1 greater than 1000 ng/mL (strongly suggesting the presence of hypersomatotropism), indicating the likely presence of a subtle phenotype in 76% of these cases.[7] Once again it seems tempting to draw comparisons to the feline hyperthyroidism situation, in which we currently more rarely see the classical hyperthyroid cat, possibly owing to increased preparedness to screen for this disease in the elderly cat and/or possible increasing prevalence.[10]

Commonly encountered signs in the acromegalic cats seen are shown in **Table 2** and **Figs. 2–4**.[4,5,9] Weight gain despite poor glycemic control should alert clinicians for the possible presence of hypersomatotropism, because weight loss would normally be expected. The existence of individual nondiabetic acromegalic cases has been mentioned in textbooks,[11] although the true prevalence of such cases is currently unknown.

Cardiomyopathies and nephropathies have been reported to ensue as part of the pathophysiology of acromegaly, presumably being induced by excess GH and IGF-1 concentrations. Because relatively few cases of feline acromegaly have been

Table 2
Commonly encountered clinical signs in feline hypersomatotropism

Clinical Sign	Timing
Polyuria/polydipsia	Early + late stages
Polyphagia (possibly extreme)	Early + late stages
Weight gain	Early + late stages
Enlarged kidneys	Early + late stages
Enlarged liver	Early + late stages
Prognathia inferior (see **Fig. 2**)	Usually only in later stages
Broad facial features (see **Fig. 3**)	Usually only in later stages
Systolic cardiac murmur	Early + late stages
Respiratory stridor (usually in later stages)	Usually only in later stages
Plantegrade stance (reversible with improved glycemic control)	Early + late stages



Fig. 2. Prognathia inferior in a cat with hypersomatotropism and acromegaly.



Fig. 3. An acromegalic cat showing an overall big stature, broad facial features, clubbed paws, and prognathia inferior.



Fig. 4. A plantegrade stance as a consequence of suboptimal glycemic control in a cat with hypersomatotropism-induced diabetes mellitus.

described thus far and most previous cases seem to have an advanced stage of hypersomatotropism-induced acromegaly, however, this assumption warrants further investigation, especially, in view of the high prevalence of concurrent disease, including cardiomyopathies and nephropathies among nonacromegalic diabetic and nondiabetic geriatric cats in general. A recent comparison of routine clinical pathology parameters between acromegalic diabetic cats and nonacromegalic diabetic cats did not reveal a greater incidence of azotemia among acromegalic cats.[12] Pancreatic abnormalities, specifically hyperplasia, do seem particularly prevalent in acromegalic cats based on post mortem examinations of patients seen in the authors' acromegalic cat clinic (**Fig. 5**).[4,10] The overall message should probably be that clinicians ought to remain open minded about the signalment and presentation of the acromegalic cat in this age of rediscovery of this endocrinopathy.

DIAGNOSIS OF HYPERSOMATOTROPISM

Routine Clinical Pathology

Routine clinical pathology will not be decisive in the diagnostic process, although can appraise the clinician of presence of any comorbidities or deleterious consequences of the hypersomatotropism. Diabetes mellitus–induced changes, including hyperglycemia, glycosuria, high cholesterol, and elevation of hepatic enzymes, can be found in hypersomatotropism, although do not help differentiate diabetes secondary to



Fig. 5. Nodular hyperplasia of the pancreas in a cat with hypersomatotropism.

hypersomatotropism from type 2 diabetes. A recent comparison study of biochemistry findings in either group, did find significantly higher total protein concentrations in acromegalic diabetic cats, which fits with the bias toward protein synthesis in hypersomatotropism. Influence of dehydration, however, quite common in diabetic animals, causes significant overlap in protein levels between the 2 groups, prohibiting its use as a discriminatory test.[12] Azotemia was previously found in 2 reports[13,14] and was suggested to be related to a GH-induced and/or IGF-1–induced nephropathy, diabetes, and/or hypertension. Interestingly, neither azotemia nor hypertension is commonly seen in the authors' clinic.[5,12] In terms of hematology findings, a nonsignificant trend toward higher hematocrit values was also apparent.[12]

Endocrine Testing: Which Test is Best for Screening?

An overview of the thus far assessed screening tests is shown in **Table 3**. Feline growth hormone (fGH; serum and plasma) and IGF-1 (serum) have been shown to be useful screening tests. A suggested growth hormone cutoff value of 10 ng/mL was shown to result in an acceptable specificity of 95% and sensitivity of 84% when using the fGH assay recently developed by the authors.[9] Feline GH also appeared relatively stable, allowing overnight transport of unseparated samples[9]; however, fGH determination is currently not commercially available. Additionally, both fGH and IGF-1 were shown to yield false-positive results in a minority of cases.[5] Cases of hypersomatotropism with a normal basal fGH concentration have yet to be documented, yet IGF-1 has been documented to be falsely negative in a minority of cases.[4,10,14] The duration of exogenous insulin administration could play an essential role in the latter, because hepatic IGF-1-production is induced via stimulation of insulin-dependent hepatic GH-receptors. An insulin-deficient state can act as an inhibitor of such IGF-1 production, resulting in low IGF-1 concentrations in diabetic patients before institution of exogenous insulin treatment or even during the first few weeks of such treatment. When screening for presence of acromegaly, these specific IGF-1 dynamics should be taken into account and repeat IGF-1 determination should be considered 6 to 8 weeks into the treatment. Alternatively, if one wishes to determine IGF-1 only once, the latter time point is recommended over the immediate time of diagnosis of diabetes mellitus. When a diabetic cat has a mild elevation of IGF-1, yet not in the acromegalic range, the clinician is faced with a dilemma. This mild elevation can be seen in uncomplicated diabetes as well as in genuine hypersomatotropism. A repeat measurement 1 or 2 months later could be considered in such cases; however, if the cat already has evidence of insulin resistance (requiring >1.5–2.0 units per kg per injection on a twice-a-day regimen), values in this grey-zone result, probably justify proceeding immediately with further hypersomatotropism diagnostics, including intracranial imaging.

Given the potential for both false positives and false negatives with either GH or IGF-1 assessment and the need for confirmatory intracranial imaging, research is currently ongoing to evaluate alternative biomarkers for feline hypersomatotropism. Because hypersomatotropism is associated with tissue growth, serum type III procollagen propeptide (PIIIP), a peripheral indicator of collagen turnover, has recently been shown to be elevated in cats with hypersomatotropism. A PIIIP concentration greater than 8 ng/mL was shown to be 100% specific for a diagnosis of hypersomatotropism, with a sensitivity of 75%.[15] Serum ghrelin, an endogenous ligand of the GH secretagogue receptor and therefore susceptible to negative feedback in a state of hypersomatotropism, has thus far not been found useful in differentiating diabetes from hypersomatotropism-induced diabetes, despite such suggestions in human hypersomatotropism.[16] The glucose suppression test (measuring GH before and after

Table 3
Overview and characteristics of endocrine screening tests for feline hypersomatotropism

Screening Test	Protocol	Interpretation	Sensitivity	Specificity
IGF-1	1. Baseline serum sample 2. Alternatively: sample after 8 wk of insulin therapy OR 2 samples: 1 before insulin therapy and 1 after 8 wk of insulin therapy	>1000 ng/mL: HS suspected, pituitary imaging indicated <1000 ng/mL, BUT insulin therapy only recently started/yet to start: repeat test in 8 wk time	☆☆☆☆	☆☆
fGH	1. Baseline serum sample fasted, morning and before receiving insulin that day	<10 ng/mL: HS unlikely >10 ng/mL: HS possible, IGF-1 and/or pituitary imaging indicated	☆☆☆☆	☆☆
IGF-1/fGH combination	1. As per above	As per above, with added specificity	☆☆☆☆	☆☆☆
PIIIP	1. Random serum sample	Only limited data available; >8 ng/mL HS likely, additional fGH, IGF-1 and/or pituitary imaging indicated	☆☆☆	☆☆☆
Glucose suppression test	1. Baseline serum fGH sample, fasted, morning and before receiving insulin that day 2. Inject intravenously 1 g/kg glucose (diluted 1:1 with sterile water) 3. Serum fGH at 30 min, 60 min, and 90 min	Only limited data available; use currently not supported	—	—
Feline ghrelin	1. Baseline fasted, morning and before receiving insulin that day	Only limited data available; use currently not supported	—	—

Abbreviations: The star rating indicates the degree of sensitivity or specificity with: ☆, indicating very poor sensitivity or specificity; ☆☆☆☆☆, indicating very good sensitivity or specificity; —, not sufficient data available; fGH, feline growth hormone; HS, hypersomatotropism; IGF-1, insulinlike growth factor 1; PIIIP, type III procollagen propeptide.

administration of glucose) is a gold standard test in the diagnosis of human hypersomatotropism, although little evidence in favor of its use in feline hypersomatotropism has as yet been published.[14,17–19]

THE ROLE OF IMAGING IN HYPERSOMATOTROPISM

Intracranial imaging (with contrast enhancement) has been proven useful in confirming the presence of hypersomatotropism, with MRI probably more sensitive than CT.[5,9,11,13,14,20] Cases with a negative CT and/or MRI have been documented, however, with the diagnosis eventually being confirmed on post mortem examination.[5] Nevertheless, if a structural pituitary abnormality is documented, this indeed provides further circumstantial evidence for the presence of hypersomatotropism, especially if there are concurrent increases in frontal bone thickness and/or evidence of soft tissue accumulation in the nasal cavity, sinuses, and pharynx.[21] However, the demonstration of a pituitary tumor as such does not provide differentiation from a nonfunctional pituitary tumor or pituitary dependent hyperadrenocorticism (PDH), especially because pituitary tumors are a relatively common type of brain tumor in the cat.[22] Additionally, cases with subtle (microscopic) acidophilic hyperplasia or microadenoma, instead of obvious (macroscopic) adenoma, might more likely show negative intracranial imaging. Dynamic intracranial imaging studies using timed injection of contrast might be of aid here.

The potential for false-negative results for intracranial imaging raises the question of the appropriate course of action when a negative image result is obtained despite the presence of a documented hormonal imbalance (elevated fGH, IGF-1, presence of diabetes). When imaging is negative, it seems more logical to have the ultimate premortem diagnosis of hypersomatotropism (and subsequent treatment decisions) rely on hormonal assessment. In conclusion, pituitary imaging is too expensive and too invasive (sedation or anesthesia needed) to be considered suitable as a *screening* test, and is ideally used as an attempt *to confirm* the disease or for preradiation or presurgical planning. Refinement of our hormonal assessment methods and increasing availability of assays probably constitutes the best way to improve the diagnosis of hypersomatotropism.

TREATMENT OPTIONS FOR HYPERSOMATOTROPISM

Treatment options for hypersomatotropism consist of medical treatment, surgical options, radiotherapy, or palliative treatment. When definitive treatment is instituted, clinicians and owners need to be vigilant for rapid changes in insulin demands should the treatment prove effective. Iatrogenic hypoglycemia is frequently encountered and home blood glucose measurement or, at least, home urine glucose screening should be considered.

Medical Treatment

In contrast to the situation in human hypersomatotropism, medical treatment options aimed at inhibiting the pituitary have not proven very successful in the cat thus far, including the use of somatostatin analogues lanreotide (Ipsen, Paris, France) and sandostatin (Novartis, Basel, Switzerland) (long-acting synthetic somatostatin analogues).[4,10,23,24] The use of dopamine agonists has not resulted in convincing improvement, yet carries the risk of a range of side effects.[4,24] One study showed that intravenous octreotide alters serum GH levels in a subset of acromegalic cats, suggesting that, at least in such subset, medical pituitary inhibition could prove beneficial.[25]

Most recently, hope for effective medical management of feline hypersomatotropism has arisen in a phase 2 clinical trial conducted by the authors using a novel somatostatin analogue (Pasireotide, Novartis), which has yielded undisputable evidence of reduction of insulin requirements in all 8 participating patients with feline hypersomatotropism, as well as diabetic remission in one of them (Stijn Niessen, DVM, PhD, DipECVIM, personal communication, 2012). The effectiveness of this drug suggests that the feline acidophilic adenoma does display somatostatin receptors, contrary to previous beliefs. Receptor mutations or predominance of certain receptor subtypes not targeted by previous somatostatin trials might form the explanation of why those previous trials proved unsuccessful.

Surgery

Hypophysectomy is considered the treatment of choice in human hypersomatotropism. After decades of this procedure being available only in the Netherlands, transphenoidal hypophysectomy has in recent years become available also in the United Kingdom (London), United States (California), and Japan. Analog to the situation in human medicine, success rates are strongly correlated with the experience of the surgeon, as well as the availability of high-quality intensive postoperative care.

The surgical approach is with the patient in a sternal position, through the cat's open mouth and a soft palatial incision to subsequently expose the sphenoid bone through the mucoperiosteum. A small drill ensures exposure of the dura mater surrounding the pituitary fossa (**Fig. 6**).[26] Perioperatively and postoperatively, desmopressin, thyroxine, and glucocorticoid supplementation should be initiated to ensure a smooth recovery of the patient. In the authors' clinic, a constant rate intravenous insulin infusion ensures reasonable glycemia preoperatively, perioperatively, and postoperatively until the patient is eating again, after which traditional insulin protocols are applied. Glucose concentrations must be very closely monitored, however, because severe clinical hypoglycemia can ensue in patients as soon as the first week after surgery. In addition, perioperatively and immediately postoperatively, an intravenous



Fig. 6. Intraoperative view during a hypophysectomy on a cat with hypersomatotropism. The soft palatial incision is being closed after removal of the cat's pituitary.

hydrocortisone constant rate infusion ensures glucocorticoid provision until the patient starts eating again, after which prednisolone (0.1 mg/kg/d) or hydrocortisone (0.5 mg/kg/d is started). The induced diabetes insipidus seems only temporary in nature in most patients, whereas secondary hypocortisolism and secondary hypothyroidism require lifelong supplementation.[26]

A recent report described the successful application of hypophysectomy in an acromegalic cat, resulting in an immediate drop of GH levels after surgery, as well as resolution of the diabetes mellitus within 3 weeks.[26] Subsequently, 5 more cases were published all showing diabetic remission rates within 4 weeks after surgery.[27] In the authors' clinic, diabetic remission has been noted as soon as 1 week after surgery. This further substantiates that early diagnosis and subsequent immediate and effective intervention increases the chance for complete diabetic remission hugely, given that sufficient beta-cell function will still be present in many of these cases. Finally, cryohypophysectomy has been reported to be successful in 2 cases.[28]

Radiation Therapy

Radiation therapy is currently still the most widely applied definitive treatment modality for feline hypersomatotropism. Indeed, it is able to reduce the size of the adenoma as well as reduce the excess hormone secretion to a certain degree in a high proportion of cases.[29,30] Evaluation of more refined protocols and "gamma-knife" technology are currently ongoing and might improve results further. Nevertheless, several important less desirable characteristics are associated with this modality: high costs, need for multiple anesthetics, and, most importantly, the response is variable and unpredictable. Some patients will start showing a treatment effect during the radiation course, others will not have a response until a year after treatment. The duration of effect is also variable. In 13 of 14 diabetic cats with hypersomatotropism receiving radiotherapy in 10 fractions, 3 times a week to a total dose of 3700 cGy (representative of many commonly used protocols), diabetic control improved, although diabetic remission occurred in only 6 cats, 3 of whom relapsed 3, 17, and 24 months after treatment.[30] Finally, radiation does not usually normalize GH and IGF-1 concentrations,[9,30] in contrast to hypophysectomy.[26,27]

Palliative Treatment

A more conservative approach ignores the underlying disease mechanism and focuses on gaining more control of the diabetes mellitus and treating possible comorbidities. Eventually most cats tend to need high dosages of insulin and/or combinations of short-acting and long-acting insulin types to ensure an adequate quality of life for both pet and owner. Nevertheless, this approach can result in an adequate level of diabetic control in a minority of cases, although careful and continued assessment of quality of life is indicated, possibly aided by quantitative tools.[31] Home monitoring of blood glucose concentrations can prove very useful to optimize dose. This is particularly relevant, as GH is secreted in a pulsatile fashion, also in case of an acidophilic adenoma, leading to variable insulin resistance and therefore variable insulin requirements. Home monitoring can prevent insulin overdose and clinical hypoglycemia at particular times of lower growth hormone concentrations. A low-carbohydrate canned diet would be advocated, as is the case in regular diabetic felines.

HYPERADRENOCORTICISM

Hyperadrenocorticism (HAC) indicates a state of excess glucocorticoid activity and can be caused by excess administration of drugs with glucocorticoid activity or

increased endogenous glucocorticoid activity (**Fig. 7**). Excess glucocorticoid activity can also result in diabetes and therefore represents another possible form of "other specific type of diabetes." Glucocorticoids are able to induce diabetes through a variety of mechanisms, including impairment of insulin-dependent glucose uptake in the periphery and enhanced gluconeogenesis in the liver.[32–36] In addition, glucocorticoids oppose several other actions of insulin, including its central inhibitory effect on appetite.[32] Finally, steroid-induced inhibition of insulin secretion of pancreatic beta-cells has also been shown to occur.[37,38]

PREVALENCE OF HYPERADRENOCORTICISM

Noniatrogenic or spontaneous hyperadrenocorticism, with or without subsequently induced diabetes, seems to be a rare condition in cats with approximately 100 cases reported in veterinary literature.[39–55] However, it is currently still unknown what proportion of the diabetic cat population, especially poorly controlled diabetic cats, has this form of diabetes induced by hyperadrenocorticism. Unfortunately, any screening studies are hampered by the lack of a specific and easily performed confirmatory test for this endocrinopathy, although a rough estimate of the likely *maximum* prevalence could be achieved by assessing urine cortisol:creatinine ratios (UCCRs) in morning urine samples collected at home from diabetic cats (see diagnostics). However, the true prevalence would be significantly lower than estimates using UCCRs, given the known lack of specificity of this test in animals with concurrent disease (ie, poorly controlled diabetes).

Iatrogenic feline hyperadrenocorticism is also rare and certainly less common than iatrogenic hyperadrenocorticism in dogs. Interestingly, 7.5% of diabetic cats included in a study concerning insured diabetic cats in the United Kingdom, had a confirmed history of glucocorticoid administration indirectly implicating glucocorticoids in the

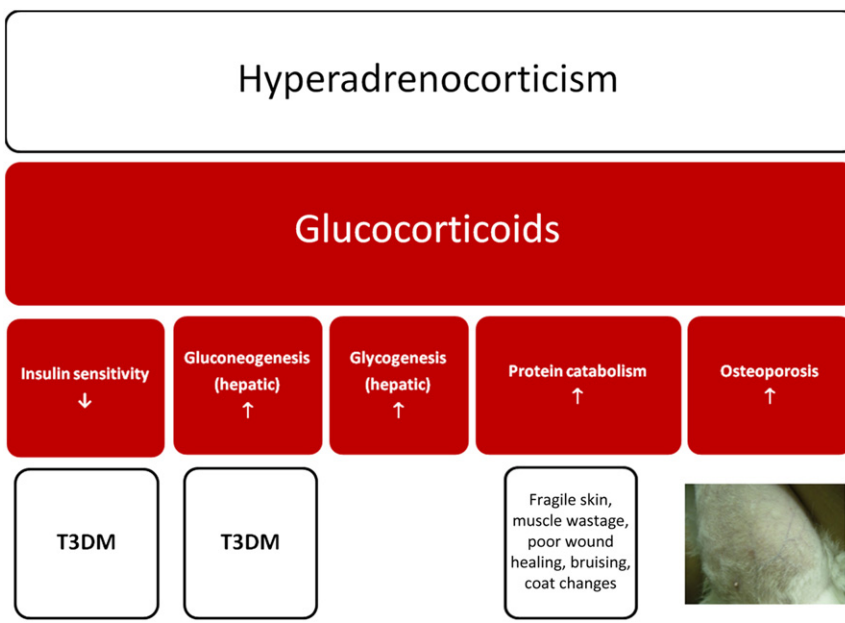


Fig. 7. Overview of pathophysiology of hyperadrenocorticism. T3DM, other specific type of diabetes/type 3 diabetes.

etiology of their diabetes (assumed type 2).[1] In another study, 4 of 12 cats on long-term steroids developed diabetes and subsequently achieved remission in a mean of 4.9 months after cessation of steroids and treatment with insulin.[56] Recent corticosteroid administration before onset of diabetes in cats has been shown to be associated with increased probability of diabetic remission.[57] In human patients, diabetes induced by iatrogenic steroid administration generally occurs in individuals with preexisting defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved.[58] The increased probability of remission raises the question of whether cats that develop diabetes following chronic steroid use represent an "other specific type of diabetes," or the steroid use just precipitated signs of diabetes when there were preexisting defects in insulin secretion, for example associated with the pathogenesis of type 2 diabetes. The fact that many cats in remission subsequently relapse provides a more convincing argument that these cats have other underlying defects in insulin secretion and their diabetes is not solely attributable to steroids. In line with the classification system used for humans, cats developing diabetes while on steroids and achieving remission with cessation of steroids and insulin treatment, should be classed as "other specific type of diabetes—subclass endocrinopathy." They should be reclassified as "type 2 diabetes," however, if they later relapse in the absence of steroids or other identifiable disease processes associated with "other specific types of diabetes."

ETIOLOGY OF HYPERADRENOCORTICISM

Just like canine hyperadrenocorticism, spontaneous feline hyperadrenocorticism is caused by either a functional pituitary tumor (PDH) oversecreting adrenocorticotropic hormone (ACTH) or a functional tumor of the adrenal cortex oversecreting hormones with glucocorticoid activity. PDH is the most prevalent form (75%–80% of cases) and is usually caused by an adenoma of the pars intermedia or pars distalis of the pituitary gland. Rare pituitary carcinomas have been described. The remaining 20% to 25% of cases have adrenal-dependent hyperadrenocorticism (ADH). Of the latter group, a benign functional adenoma of the cortex of one of the adrenals is most likely (65%) with a malignant cortical carcinoma affecting a minority of cats with ADH.[39,41,55]

Variations of these etiologies have also been described in individual cases. These include unilateral and bilateral cortical carcinomas producing excess sex hormones with glucocorticoid effects (eg, progesterone, androstenedione, testosterone), a case of a diabetic cat with assumed ACTH-independent cortisol production caused by excess alpha-MSH production by a pituitary tumor exerting glucocorticorticotropic effects, and a double pituitary adenoma overproducing both GH and ACTH causing acromegaly and hyperadrenocorticism.[39–49] Finally, rare cases of multiple-endocrine neoplasia have been described to include hyperadrenocorticism.[43,51]

Although cats are more resistant to the effects of steroids, iatrogenic hyperadrenocorticism should be considered in any cat that becomes diabetic while receiving glucocorticoid supplementation. Such supplementation could include topical preparations for dermatologic (including ear disease) or ophthalmic disease. Nevertheless, an underlying predisposition for type 2 diabetes should be suspected in cats with onset of diabetes after exogenous steroid administration, which subsequently proves permanent despite quick withdrawal of these exogenous glucocorticoids, or in cats that achieve remission but subsequently relapse in the absence of steroids.

The excess of exogenous or endogenous glucocorticoid activity will usually result in a range of changes in the cat's body, all related to the physiologic function of glucocorticoids (see **Fig. 7**). Marked insulin resistance can therefore ensue and it is

unsurprising that 80% to 90% of cases with hyperadrenocorticism are presented with signs referable to overt diabetes.[39–41,55,59]

SIGNALMENT AND PRESENTATION OF HYPERADRENOCORTICISM

A comparison of basic characteristics between hypersomatotropism and hyperadrenocorticism is shown in **Table 1**. Frequent physical examination findings are shown in **Box 1**.[39–55] Like with hypersomatotropism, most cats with hyperadrenocorticism will present with signs referable to diabetes (polyuria, polydipsia, polyphagia and peripheral neuropathy), which, as time goes on, often turns out to be insulin resistant in nature. Nevertheless, the insulin requirements tend to be less extreme than those found in some cats with hypersomatotropism and indeed not all diabetic cats with hyperadrenocorticism are in fact insulin-resistant. Interestingly, weight loss, instead of weight gain, is most common with hyperadrenocorticism. This therefore represents a significant difference compared with the dog and a useful difference in differentiating from the diabetic cat with hypersomatotropism (**Table 4**).

A minority of cats with hyperadrenocorticism will present differently and focus might lie instead on dermatologic abnormalities, such as skin fragility or polyphagia and weight gain, instead of diabetes-related clinical signs. The perceived lack of polyuria and polydipsia in the latter cases without overt diabetes illustrates the inherent resistance cats have (compared with dogs) to the glucocorticoid-induced inhibition of secretion and action of antidiuretic hormone.[39] Polyuria and polydipsia tends to ensue only once diabetes has arisen.

Specific signs that cats share with their canine counterparts include abdominal enlargement or pot-bellied appearance (**Fig. 8**), panting, muscle atrophy, unkempt hair coat (**Fig. 9**), bilateral symmetric alopecia, and predisposition for infections (urinary tract, skin, abscesses, respiratory tract, toxoplasmosis).[39,44,55] More specific to the cat is the so-called "fragile skin syndrome" (**Figs. 10** and **11**), which is thought to relate to the protein catabolism and can result in tearing of the skin under otherwise innocuous circumstances, such as self-grooming or owners grasping their cat. Also

Box 1
Reported physical examination findings in hyperadrenocorticism

- Pot belly (see **Fig. 8**)
- Unkempt coat (see **Fig. 9**)
- Muscle wastage
- Bilateral symmetric hair thinning, seborrhea, or alopecia
- Thin skin (see **Figs. 8** and **10**)
- Change in coat color (see **Fig. 11**)
- Ecchymoses (see **Fig. 10**)
- Inappropriate body condition score
- Cutaneous lacerations or fragile skin (see **Fig. 11**)
- Obesity/weight gain (less frequent)
- Hepatomegaly
- Signs of (recurrent) infection (including abscess)
- Plantegrade stance (see **Fig. 9**)

Table 4
Clues toward the differentiation between the diabetic cat with HS and the diabetic cat with HAC

HS	HAC
Frequent weight gain	Frequent weight loss
Lack of dermatologic signs apart from possible unkempt coat	Frequent dermatologic signs
Lack of muscle wasting	Frequent muscle wasting
Ultimately severe or extreme insulin resistance	Lack of insulin resistance, or, more frequent, modest insulin resistance
Infrequent generalized poor condition	Frequent generalized poor condition
Absence of diabetes very rare	Absence of diabetes possible
IGF-1 elevated	IGF-1 usually not elevated

Abbreviations: HAC, hyperadrenocorticism; HS, hypersomatotropism; IGF-1, insulinlike growth factor 1.

in contrast to the dog, cats with hyperadrenocorticism have not been reported to develop calcinosis cutis. Cats can, however, develop hair coat color changes (see **Fig. 11**).

Finally, rare cases in which cats presented with blindness (caused by a pituitary macroadenoma or hypertension induced),[54] abnormal behavior, compulsive walking, circling, and continuous vocalization have also been reported.[44,45] Virilization has been encountered in cases with sex hormone–secreting (androstenedione and testosterone) adrenal carcinomas, which might be picked up by observing spines on the penis of a castrated male cat.



Fig. 8. Pot belly and thin skin appearance of a cat with hyperadrenocorticism.



Fig. 9. Unkempt hair coat and plantegrade stance in a cat with hyperadrenocorticism.

DIAGNOSIS OF HYPERADRENOCORTICISM

Routine Clinical Pathology

In most cases, changes in hematology, biochemistry, and urine analyses are attributable to diabetes. A stress leukogram is inconsistently present, although elevation of neutrophils might also be related to a secondary infection evoked by decreased



Fig. 10. Pot belly, ecchymosis, and thin skin appearance of a cat with hyperadrenocorticism.



Fig. 11. Coat color changes induced by hypercortisolemia caused by PDH, as well as evidence of fragile skin syndrome on the left hind paw.

immunity or bacterial infection of skin wounds. Given the lack of a steroid-inducible ALP isoenzyme and therefore in contrast to the situation in the dog, less than one-fifth of cats with hyperadrenocorticism will show elevation of alkaline phosphatase (ALP). If found, it will be related to the unregulated diabetes. Another interesting difference with canine hyperadrenocorticism is the relative rareness of finding dilute urine in cats with hyperadrenocorticism, demonstrating the lack of effect of cortisol on feline ADH secretion and/or sensitivity. Only 1 of 43 cats reported in a hyperadrenocorticism case series had a urine specific gravity of less than 1.043,[39] although this parameter will also be partially affected by the presence of glucosuria in many cases. Proteinuria can also be encountered.

Endocrine Testing: Which Test is Best for Screening?

Endocrine tests that may be useful in substantiating a diagnosis of feline hyperadrenocorticism include the low-dose dexamethasone suppression test (LDDST), the ACTH stimulation test, and the UCCR. The latter can be combined with the administration of oral dexamethasone. The advantages and disadvantages of each screening test are discussed in the following sections. The protocols and interpretation of each test are described in **Table 5**, as well as an indication of each test's characteristics in terms of sensitivity and specificity. As is the case with almost any endocrine test, as well as any diagnostic test in general which is not 100% accurate, these diagnostics will demonstrate a superior positive predictive value only when used when the clinical picture sufficiently suggests the possible presence of hyperadrenocorticism. Conversely, also given the low prevalence of feline hyperadrenocorticism in general, routine screening in clinically unremarkable diabetic cats is therefore not advocated.

The LDDST

Many consider the LDDST the test of choice for diagnosis of feline hyperadrenocorticism. Clinicians should note that a higher dose of dexamethasone (0.1 mg/kg intravenously) is used than in the dog, because a high proportion of normal cats will not show suppression when using the traditional lower dose (0.01 mg/kg).[39,59,60] Intramuscular

Table 5
Overview and characteristics of endocrine screening tests for feline hyperadrenocorticism

Screening Test	Protocol	Interpretation	Sensitivity	Specificity
LDDST	1. Baseline serum cortisol (t = 0) 2. Intravenous 0.1 mg/kg dexamethasone (or intramuscular) 3. Serum cortisol t = 4 and 8 h	No suppression at t = 4 and/or 8 h (cortisol <35 nmol/or 1.3 μg/dL): HAC possible	☆☆☆☆☆	☆☆
ACTH stim	1. Baseline serum cortisol (t = 0) 2. Intravenous 125 μg synthetic ACTH (or intramuscular) 3. Timings post-ACTH sample serum cortisol t = 60 min (recommendations vary according to source, please consult your local laboratory, some suggest adding time points t = 30, 90 min, or even 120 min, the latter particularly when using compounded ACTH)	Post-ACTH cortisol > upper end reference interval: HAC possible Modest, suppressed/flatline response (lack of stimulation): iatrogenic HAC possible as well as sex hormone–secreting ADH (consider requesting additional adrenal hormones)	☆	☆☆☆☆
UCCR	1. Home-collected morning sample 2. Kept in fridge until analysis 3. Ideally multiple samples	$\geq 3.6 \times 10^{-5}$ suggestive of HAC $\leq 1.3 \times 10^{-5}$ unlikely cortisol producing HAC	☆☆☆☆☆	☆
UCCR with oral dexamethasone suppression (as screening test)	1. Two at-home collected morning samples for UCCR: calculate average 2. Owner administers 0.5 mg dexamethasone orally at 12 PM, 6 PM, and 12 midnight 3. Next morning: home-collected morning sample for UCCR	Average of 2 initial samples $\geq 3.6 \times 10^{-5}$ suggestive of HAC ≤50% suppression UCCR 3rd sample: seen with most ADH cases and 25% of PDH cases	☆☆☆☆	☆☆
POMC (please note: data based on 1 small study only)	1. Basal EDTA blood sample 2. Immediate centrifugation at 4°C 3. Plasma transferred to plastic tubes and stored at -80°C until analysis/transported on dry ice	High plasma concentration of ACTH precursors in cats (>100 pmol/L) is highly suggestive of PDH	☆☆☆☆	☆☆☆☆

Abbreviations: The star rating indicates the degree of sensitivity or specificity with: ☆, indicating very poor sensitivity or specificity; ☆☆☆☆☆, indicating very good sensitivity or specificity; ACTH, adrenocorticotrophic hormone; ACTH stim, ACTH stimulation test; ADH, adrenal dependent HAC; EDTA, ethylenediaminetetraacetic acid; HAC, hyperadrenocorticism; LDDST, low-dose dexamethasone suppression test; PDH, pituitary dependent HAC; POMC, pro-opiomelanocortin; UCCR, urine cortisol:creatinine ratio.

injection could be considered in particularly fractious cats, although the risk for false-positive hyperadrenocorticism screening testing will also be increased in this patient cohort.

The protocol is outlined in **Table 5**. Suppression at the intermediate point (often 4 hours), but especially at the final point (8 hours) (usually < ±40 nmol/L but dependent on the laboratory) is suggestive of absence of hyperadrenocorticism. It should be noted that although virtually all ADH cases will not show such suppression, there might be some PDH cases that will. In the latter case, clinical judgment will have to be used to establish the need for further testing. The use of an LDDST using the canine dose of 0.01 mg/kg dexamethasone has been suggested in such cases, although seems not helpful in the authors' opinion given the lack of suppression in a proportion of normal cats.

The ACTH stimulation test

In up to two-thirds of cats with hyperadrenocorticism, cortisol concentrations during an ACTH stimulation test are within the normal reference range, which demonstrates the lack of sensitivity of this particular endocrine test for feline hyperadrenocorticism. The test remains useful in case of iatrogenic hyperadrenocorticism, where we expect a suppressed stimulation result in conjunction with a history of glucocorticoid exposure (including topical). The test might also prove useful when dealing with adrenal tumors producing other adrenal hormones, such as 17-hydroxyprogesterone, estradiol, androstenedione, progesterone, and testosterone. There is therefore still some advantage to using the ACTH stimulation test, as test results might suggest the presence of such atypical adrenal tumor through the presence of modest or even suppressed post-ACTH cortisol concentrations in a cat with clinical signs of hyperadrenocorticism. The laboratory can then be asked to use the already submitted serum sample for further assessment of these other adrenal hormones. In these cases, the basal serum samples are often already conclusive, showing extremely high concentrations of one of these cortisol precursors and in fact only little further increase in concentration is seen in the post-ACTH samples. Gray-zone elevations in these concentrations should be assessed with caution, as there is significant scope for healthy animals to show a concentration just outside the reference interval. The additional advantage of the ACTH stimulation test is its shorter duration (compared with the LDDST) and the possibility to inject the ACTH intramuscularly as well as intravenously. However, results of one study confirmed that intravenous administration of cosyntropin induced significantly greater and more prolonged adrenocortical stimulation than intramuscular administration.[61,62] Clinicians should bear in mind the timing for intravenous protocols versus intramuscular protocols in cats, and the difference in timing of post-ACTH sample collection in cats compared with dogs, because of the more variable timing of maximal stimulation of the adrenals in cats compared with dogs (see **Table 5**).

UCCR

UCCR is a useful screening test for hyperadrenocorticism.[39,63,64] Collection of a morning sample at home will help minimize the influence of stress on the test's results.[65] The test is the most sensitive screening test, and therefore a negative result makes hyperadrenocorticism unlikely. Hyperadrenocorticism, but also any concurrent illness (including hyperthyroidism) and stress could result in an elevated UCCR.[63–66] The test can be combined with the oral administration of dexamethasone to improve specificity (although when used in this fashion will lose some sensitivity), although mainly helps by concurrently attempting to differentiate PDH from ADH.

Plasma ACTH Precursors

ACTH is derived from its precursor, pro-opiomelanocortin (POMC), which is first processed to pro-ACTH and then cleaved to ACTH by the prohormone convertase 1 (PC1). Plasma ACTH precursor (POMC and pro-ACTH) concentrations have been shown to be high in large or aggressive pituitary corticotrophic tumors in both humans and dogs and recently also in 8 of 9 cats with PDH. This small study has provided the only data thus far, and therefore more rigorous assessment is required to determine the specificity and sensitivity for feline PDH.[67]

Endocrine Testing: Which Test is Best for Differentiating PDH from ADH in Cats?

As is the case with canine hyperadrenocorticism, performing discriminatory tests is a wise investment of time and money and therefore highly recommended. A cat with PDH will have a different prognosis and will face different long-term complications than a cat with ADH; additionally, the gold standard treatment is different for each subset of diseases (see later in this article). Finally, the response to medical treatment will likely be different in each patient category.

The main discriminatory tests are shown in **Table 6**, alongside the most popular protocols and main (dis)advantages. Discriminatory tests should be performed only once a diagnosis of hyperadrenocorticism has been reached on the basis of clinical signs and a positive screening test. The exception is the UCCR with oral dexamethasone suppression, which could serve both functions, although further validation of this test is desirable.

THE ROLE OF IMAGING IN HYPERADRENOCORTICISM

The role of imaging is traditionally thought most useful in the discriminatory phase of the diagnostic process (see **Table 6**). Imaging of adrenals and/or pituitary could also serve the role of substantiating a diagnosis of hyperadrenocorticism in the first instance. Nevertheless, it seems more logical to use functional (hormonal) tests for this, rather than imaging only, because the latter provides purely structural assessment and therefore can provide only indirect evidence for a diagnosis of hyperadrenocorticism. In feline hyperadrenocorticism, pituitary imaging (using CT or MRI) lacks the sensitivity that endocrine testing can offer the clinician (45% of cats with PDH had a normal CT)[39] and is usually more expensive, as well as requiring sedation/anesthesia. Additionally, a misdiagnosis could result in cases with nonfunctional pituitary tumors or nonfunctional adrenal enlargements (“incidentelomas”) when endocrine testing is omitted.

Nevertheless, during the discriminatory phase, performing an abdominal ultrasound in a cat suspected of hyperadrenocorticism represents a wise investment. The adrenals in the cat have been reported to be easier to image than in dogs, although this obviously remains operator and equipment dependent.[39,68] Visualization of the adrenal glands will be informative in terms of differentiating PDH from ADH. On the premise of cats with ADH having one large adrenal/adrenal mass (**Fig. 12**) and one small one, versus cats with PDH having equal-sized to normal or enlarged adrenals (**Fig. 13**), 34 of 41 cats (83%) were correctly diagnosed in one study.[39] Abdominal ultrasound therefore seems a good discriminatory tool. Nevertheless, 10% had misleading results, suggesting a healthy dose of caution should be maintained. Ultrasound-guided biopsy of adrenal masses is possible, although not without danger (especially hemorrhage, although also risk of failure to reach a histologic diagnosis) and one could question the need for this, if adrenalectomy represents the gold-standard treatment option for ADH.

Table 6
Overview and characteristics of discriminating tests for feline hyperadrenocorticism

Differentiating Test	Protocol	Interpretation	Advantage	Disadvantage
HDDST	1. Baseline serum cortisol (t = 0) 2. Intravenous 1.0 mg/kg dexamethasone (or intramuscular) 3. Serum cortisol t = 4 and 8 h	If suppression >50% is seen, ADH unlikely	Easy to perform	In-hospital: stress 50% of PDH cats do not show suppression
UCCR with oral dexamethasone suppression (as differentiating test)	1. Two at-home collected morning samples for UCCR: calculate average 2. Owner administers 0.5 mg dexamethasone orally at 12 PM, 6 PM, and 12 midnight 3. Next morning: home collected morning sample for UCCR	75% of cats with PDH will show >50% suppression of the average UCCR	At home: less influence of stress Can serve as screening test and as discriminating test	25% of PDH cats do not show suppression
Endogenous ACTH	1. Usually collected in EDTA-collection tube 2. Put immediately on ice 3. Plasma separated and stored at –80°C 4. Transported to laboratory on dry ice 5. Exact protocol to be verified with laboratory performing the assay	If high or high normal: PDH likely If low or low normal: ADH likely	Only 1 sample needed	Unstable hormone: false low results (special sampling and transport conditions crucial, contact laboratory)

Adrenal size and morphology on abdominal ultrasound or CT	1. Measurements of adrenal width are taken 2. Structure of adrenals is assessed 3. Includes assessment for vena cava invasion	Bilaterally enlarged adrenals suggestive of PDH One large adrenal and small contralateral adrenal suggestive of ADH Vena cava invasion suggests adrenal carcinoma	Availability Vena cava invasion or evidence of metastases suggest presence of a carcinoma and informs treatment decisions Other causes of insulin resistant diabetes can be screened for (eg, pancreatitis)	Equipment and experience needed
Pituitary size and morphology on intracranial imaging (CT, MRI)	1. Imaging of the sella turcica 2. Precontrast and postcontrast enhancement	If macroadenoma present (pituitary height >3 mm) usually definitive	If no macroadenoma present, abdomen can also be imaged using the same modality screening for ADH and PDH Essential step for planning of hypophysectomy or radiation therapy	Limited availability Costs Need for sedation or anesthesia Micro-adenoma (50% of PDH cases) could be missed/limited sensitivity Rare immediate contrast side effects (usually only limited to waking up from sedation and vomiting)
POMC (please note: data based on 1 small study only)	1. Basal EDTA blood sample 2. Immediate centrifugation at 4°C 3. Plasma transferred to plastic tubes and stored at –80°C until analysis	If high: PDH likely	Only 1 sample needed	Not validated as differentiating test Unstable hormone: false low results (special sampling and transport conditions crucial, contact laboratory)

Abbreviations: ACTH, adrenocorticotrophic hormone; ADH, adrenal dependent HAC; EDTA, ethylenediaminetetraacetic acid; HAC, hyperadrenocorticism; HDDST, high-dose dexamethasone suppression test; PDH, pituitary dependent HAC; POMC, pro-opiomelanocortin; UCCR, urine cortisol:creatinine ratio.

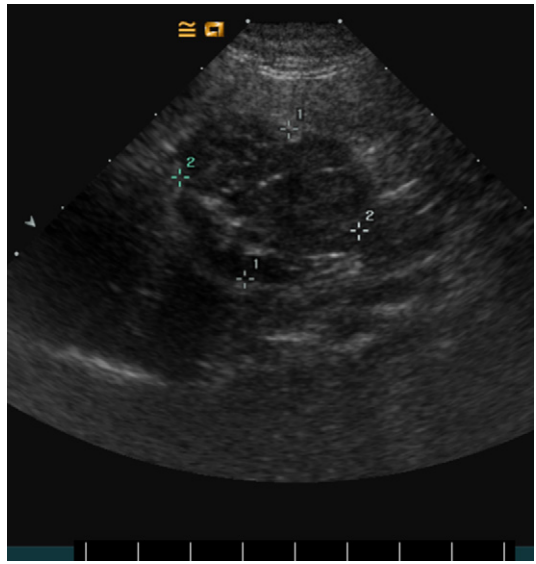


Fig. 12. Ultrasonographic evidence of an adrenal tumor in a cat with ADH.

Abdominal radiography adds little value to the diagnostic process, especially when abdominal ultrasound is available, with the exception of large adrenal tumors, which can sometimes be seen on regular radiographs. It is also important to emphasize that adrenal gland calcification can occur in cats as part of the normal aging process and does not indicate presence of an adrenal tumor as such.

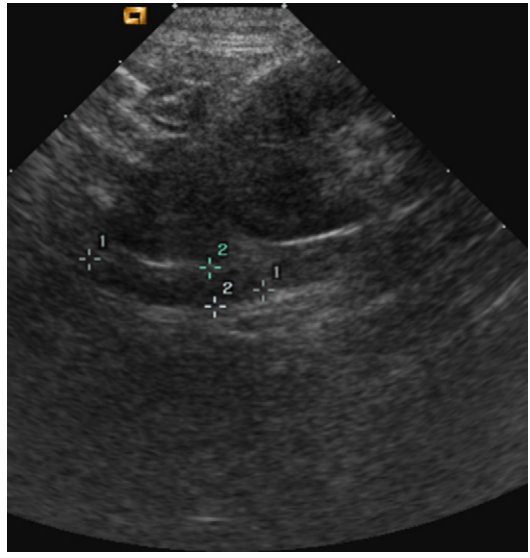


Fig. 13. Location and measurements of the adrenal gland in a cat with PDH. Both adrenals were homogeneously enlarged and a pituitary tumor was evident on a CT scan. Please note the location of the adrenal (*middle*) in relation to the kidney (*right top*).

Abdominal CT is increasingly being used for a variety of diseases affecting the abdomen and can also prove useful in the assessment of adrenal morphology, as well as assessment for vena cava invasion or metastases from an adrenal carcinoma (**Fig. 14**). In the differentiation process, both the pituitary and the adrenals could be imaged in one CT session.

Finally, a sex hormone–secreting tumor should be suspected in cats with clinical signs of hyperadrenocorticism and an adrenal mass on ultrasonography or CT, yet normal or even suppressed cortisol results.

TREATMENT OPTIONS FOR HYPERADRENOCORTICISM

Hyperadrenocorticism treatment options consist of medical treatment, surgical options, radiotherapy, and palliative treatment. As with feline hypersomatotropism, when treatment is initiated, clinicians and owners need to be vigilant for rapid changes in insulin demands. Which of the treatment options is preferred depends on the nature of the hyperadrenocorticism (ie, PDH vs ADH), hence highlighting the importance of the discrimination process.

Medical Treatment (PDH and ADH)

Medical treatment could be considered if (1) a definitive treatment option (hypophysectomy or adrenalectomy) is declined; (2) in the preoperative period to improve patient health, especially in terms of improving wound healing; (3) preradiation, periradiation, and postradiation (PDH) to assist in controlling signs; and (4) as a palliative option for cats with metastatic disease. Dosing protocols, mechanisms of action, and main (dis) advantages are shown in **Table 7**; however, currently, the authors recommend using



Fig. 14. CT reconstruction of the abdomen of a cat with ADH. A large adrenal tumor is apparent cranial to the right kidney.

Table 7
Overview and characteristics of medical treatment options for feline hyperadrenocorticism

Drug	Protocol	Mechanism of Action	Advantage	Disadvantage
Trilostane	1. 10 mg SID PO 2. ACTH stim after 14 d (4 h post pill) 3. Increase to 10 mg BID or 20 mg SID if necessary 4. ACTH stim after 14 d 5. Increase further as required on basis of clinical image and post-ACTH stim serum cortisol concentration (authors' target range: 50–150 nmol/L)	Steroidogenesis enzyme inhibitor (3-beta-hydroxysteroid-dehydrogenase)	Most effective of all medical options In principle, reversible action	Has no antineoplastic effect Limited experience in cats Lack of knowledge of pharmacokinetics, including impact of renal disease Extremely rare sudden death described in dogs may also occur in cats
Mitotane (not recommended)	25 mg/kg BID PO	Adrenocorticolytic	Has antineoplastic effect Widely available	Cats are much less sensitive to its effects than dogs: likely ineffective Chlorinated hydrocarbon sensitivity of cats (although rarely reported) Limited experience in cats
Ketoconazole (not recommended)	1. 5 mg/kg BID PO for 7 d, then 10 mg/kg BID 2. 14 d: ACTH stim 3. If no result: 15 mg/kg BID	Steroidogenesis enzyme inhibitor (targets imidazole ring and cytochrome P450)	Widely available In principle, reversible action	Cats are less sensitive to its effects than dogs: likely insufficient suppression Recognized ketoconazole side effects Limited experience in cats
Metyrapone (if trilostane not available)	1. 30 mg/kg BID PO 2. ACTH stim after 14 d 3. Increase dose gradually if needed 4. Recommended not to exceed 70 mg/kg BID	Steroidogenesis enzyme inhibitor (11-beta-hydroxylase)	Has shown some efficacy In principle, reversible action	Lack of efficacy in a proportion of cats Vomiting and inappetence Limited experience in cats

Abbreviations: ACTH, adrenocorticotrophic hormone; ACTH stim, ACTH stimulation test; BID, twice a day; PO, by mouth; SID, once a day.

trilostane above all other medical options, given its superior efficacy, relative lack of side effects, and ease of use. For cats that prove sensitive to trilostane, a good quality of life can be achieved long term in a significant proportion of cats (Drs Stijn Niessen, David Church, and Yaiza Forcada, personal communication, 2013).[49,69,70] When treating with trilostane, the authors aim for clinical improvement in conjunction with post-ACTH serum cortisol concentrations between 50 and 150 nmol/L.

Surgery

Hypophysectomy (PDH)

As is the case for feline hypersomatotropism, hypophysectomy is considered the treatment of choice in human, canine, and feline PDH. The largest case series to date consisted of 7 cats with PDH,[46] but likely underestimates the ultimate potential of this procedure, as experience in Dr Meij and colleagues' institution has since increased further, alongside the success rates. It still represents a major intervention; one cat in this initial series did not recover from anesthesia, and a second cat developed neurologic abnormalities 2 weeks after surgery. Nevertheless, the remaining 5 cats showed clinical and clinical pathologic resolution of their hyperadrenocorticism. Given the nature of the procedure (the pituitary is approached through an incision in the soft palate), oronasal fistulas can occur (and resulting chronic rhinitis), although increased experience will reduce the frequency of such occurrence. More information can be found in the hypersomatotropism surgery section earlier in this article.

Unilateral or bilateral adrenalectomy (ADH or PDH)

A second preferred surgical option for PDH constitutes bilateral adrenalectomy and, for ADH, unilateral adrenalectomy. The procedure requires less expertise than a hypophysectomy, although perioperative and postoperative management are equally important and (hypercortisolemia-associated) impaired wound healing can represent an added level of difficulty. In the authors' institution, a hydrocortisone infusion is started as soon as the surgeon starts working on the adrenal(s) and is continued until the patient is eating again after the procedure. At this stage, the patient is transitioned to oral glucocorticoids, either a low dose of prednisolone (0.1 mg/kg once a day) or hydrocortisone (0.5 mg/kg once a day). Whenever possible, presurgical treatment with trilostane is advocated by the authors to ensure normalization of the wound-healing processes. Vitamin A supplementation has also been used on the basis of the theoretical advantage in terms of beneficial effects on wound healing. When impaired wound healing and/or skin fragility is a great concern, a flank incision approach to the adrenal(s) is often preferred, as this might reduce the risk of wound breakdown postoperatively given the decreased tension on the wound compared with a midline incision approach. Laparoscopy can prove even more advantageous in terms of wound healing and has been shown to be feasible for the purpose of adrenalectomy in a cat with ADH.[71]

In case of bilateral adrenalectomy for PDH, the patient is then treated as an Addisonian animal. In case of unilateral adrenalectomy for ADH, glucocorticoid treatment is continued in the immediate postoperative period, and then tapered gradually over 6 weeks so the remaining adrenal gland can gradually resume glucocorticoid production. Basal cortisol checks on serum samples taken 12 hours after the administration of prednisolone or hydrocortisone can guide the assessment of the activity levels of this contralateral adrenal during the last part of this period and can inform the ultimate decision to stop medication completely. Alternatively, an ACTH stimulation test can give additional information about this adrenal, and will be less influenced by prior chronic exogenous steroid administration. If this approach fails (flatline ACTH

stimulation test results are consistently seen even when the cat has been on a very low dose of steroids for a month), a final approach would be to taper the exogenous glucocorticoids gradually and completely anyway and then perform a basal cortisol or ACTH stimulation test 4 weeks after cessation of the steroids to document adequate functioning of the remaining adrenal. In the latter case, it is advisable to ensure that the cat's owners will have steroids available at home, to be given in case of an Addisonian crisis.

Radiation Therapy (PDH)

Radiation therapy is also discussed in the feline hypersomatotropism section earlier in this article. In summary, the unreliability in terms of response to treatment is the greatest pitfall of using this modality, as is the case when treating feline hypersomatotropism.[39] Hypophysectomy and bilateral adrenalectomy are therefore often preferred. When this modality is used for treatment of PDH, concurrent start of trilostane treatment is often indicated to reliably and immediately start controlling the ill effects of the hypercortisolemic state.

Palliative Treatment

Unlike the situation in hypersomatotropism and given the more readily available and often effective medical treatment or surgical options for hyperadrenocorticism (trilostane, adrenalectomy), treating the diabetes without addressing the underlying endocrinopathy (hyperadrenocorticism) is usually not indicated. Additionally, hyperadrenocorticism tends to result in more acute complications with seriously debilitating effects compared with feline hypersomatotropism, and intervention to reduce the endogenous cortisol levels is therefore usually more urgently needed. Meticulous wound management might be indicated in case of fragile skin syndrome–associated wounds, as well as adequate prevention and treatment and management of opportunistic infections and screening for hyperadrenocorticism-associated hypertension and proteinuria. A low carbohydrate canned diet recommended for diabetic felines, would be advocated to reduce demand on beta cells to produce insulin.

DIFFERENTIATING FELINE HYPERSOMATOTROPISM AND FELINE HYPERADRENOCORTICISM

Because both hypersomatotropism and hyperadrenocorticism can present with insulin-resistant diabetes and a pituitary tumor, it is of practical importance to be able to differentiate hypersomatotropism from hyperadrenocorticism. **Table 4** provides useful hints toward the differentiation process.

QUALITY OF LIFE AND PROGNOSIS IN FELINE HYPERSOMATOTROPISM AND HYPERADRENOCORTICISM

Continuous quality of life assessment is crucial to ensure the patient is managed in the most appropriate way, and if necessary, a timely decision to consider alternative treatment options or euthanasia is made by all parties involved. Feline hyperadrenocorticism tends to more acutely cause severe quality-of-life issues when left untreated or if treatment fails. In contrast, quality of life will be affected in a more chronic and slowly progressive fashion in feline hypersomatotropism when left unattended. Because both diabetic cats with hyperadrenocorticism and those with hypersomatotropism can have suboptimal glycemic control, a diabetes-specific quality-of-life quantification tool is used in the authors' diabetic cat clinic.[31] Using such a tool regularly facilitates and stimulates conversations between owners and clinicians, as well as

enables more objective tracking of the quality of life of these diabetic patients, especially when undergoing treatment.

Because feline hyperadrenocorticism is more debilitating in nature, traditionally a guarded to grave prognosis has been suggested. The advent of advanced surgical techniques (hypophysectomy), improved perioperative protocols for bilateral adrenalectomy, as well as trilostane treatment, justify modifying this perception, because, when the hypercortisolemia is reduced effectively, a good quality of life can be achieved for a long period. Similarly, advances in the treatment of feline hypersomatotropism, especially in terms of increased availability of hypophysectomy and identification of effective somatostatins, will likely lead to modification of expected life expectancy and life quality expectations. When effective treatment is initiated early enough, an improved quality of life and even diabetic remission can be achieved.

REFERENCES

1. McMann TM, Simpson KE, Shaw DJ, et al. Feline diabetes mellitus in the UK: the prevalence within an insured cat population and a questionnaire-based putative risk factor analysis. J Feline Med Surg 2007;9:289–99.
2. Rand JS, Fleeman LM, Farrow HA, et al. Canine and feline diabetes mellitus: nature or nurture? J Nutr 2004;134:2072S–80S.
3. Forcada Y, Holder A, Jepson R, et al. A missense mutation in the coding sequence of MC4R (MC4R: C.92 C4T) is associated with diabetes mellitus in DSH cats. J Vet Intern Med 2011;25:681.
4. Niessen SJ. Feline acromegaly: an essential differential diagnosis for the difficult diabetic. J Feline Med Surg 2010;12(1):15–23.
5. Niessen SJ, Petrie G, Gaudiano F, et al. Feline acromegaly: an underdiagnosed endocrinopathy? J Vet Intern Med 2007;21(5):899–905.
6. Elliott DA, Feldman EC, Koblik PD, et al. Prevalence of pituitary tumors among diabetic cats with insulin resistance. J Am Vet Med Assoc 2000;216(11):1765–8.
7. Niessen SJ, Forcada Y, Jensen K, et al. Routine screening of diabetic cats for acromegaly: overdue or overkill? [abstract]. J Vet Intern Med 2011;25:1489–90.
8. Berg RI, Nelson RW, Feldman EC, et al. Serum insulin-like growth factor-I concentration in cats with diabetes mellitus and acromegaly. J Vet Intern Med 2007; 21(5):892–8.
9. Niessen SJ, Khalid M, Petrie G, et al. Validation and application of an ovine radioimmunoassay for the diagnosis of feline acromegaly. Vet Rec 2007;160:902–7.
10. Niessen S. Acromegaly in cats: what do we know & what don't we know. In: ACVIM Forum Proceedings Committee, editor. Proceedings of the American College of Veterinary Medicine Annual Forum. Denver (CO): CD-ROM; 2011.
11. Feldman EC, Nelson RW. Disorders of growth hormone. In: Feldman EC, Nelson RW, editors. Canine and feline endocrinology and reproduction. 3rd edition. St Louis (MO): Saunders; 2004. p. 69–80.
12. Niessen SJ, Petrie G, Gaudiano F, et al. Routine clinical pathology findings in feline acromegaly. In: BSAVA Congress Proceedings Committee, editor. Proceedings of the British Small Animal Veterinary Association (BSAVA) congress. BSAVA, Gloucester, UK, Birmingham (United Kingdom): 2007. p. 482.
13. Peterson ME, Taylor RS, Greco DS, et al. Acromegaly in 14 cats. J Vet Intern Med 1990;4:192–201.
14. Norman EJ, Mooney CT. Diagnosis and management of diabetes mellitus in five cats with somatotrophic abnormalities. J Feline Med Surg 2000;2:183–90.

15. Niessen SJ, Forcada Y, Church DB. Serum type III procollagen propeptide: an alternative measure of growth hormone bioactivity bioactivity in cats with diabetes mellitus and hypersomatotropism. J Vet Intern Med 2012;26(6):1520 TBC.
16. Jensen K, Forcada Y, Glanemann B, et al. Physiology and diagnostic potential of serum ghrelin in cats with diabetes mellitus and hypersomatotropism. J Vet Intern Med 2012;26b(6):1519 TBC.
17. Chang-DeMoranville BM, Jackson IM. Diagnosis and endocrine testing in acromegaly. Endocrinol Metab Clin North Am 1992;21:649–68.
18. Eigenmann J, Wortman J, Haskins M. Elevated growth hormone levels and diabetes mellitus in a cat with acromegalic features. J Am Anim Hosp Assoc 1984;20:747–52.
19. Kokka N, Garcia JF, Morgan M, et al. Immunoassay of plasma growth hormone in cats following fasting and administration of insulin, arginine, 2-deoxyglucose and hypothalamic extract. Endocrinology 1971;88:359–66.
20. Posch B, Dobson J, Herrtage M. Magnetic resonance imaging findings in 15 acromegalic cats. Vet Radiol Ultrasound 2011;52(4):422–7.
21. Fischetti AJ, Gisselman K, Peterson ME. CT and MRI evaluation of skull bones and soft tissue in six cats with presumed acromegaly versus 12 unaffected cats. Vet Radiol Ultrasound 2012;53(5):535–9 online only at moment.
22. Troxel MT, Vite CH, Van Winkle TJ, et al. Feline intracranial neoplasia: retrospective review of 160 cases (1985-2001). J Vet Intern Med 2003;17(6):850–9.
23. Timian J, Lunn KF. Evaluation of a long-acting somatostatin receptor ligand for the treatment of feline acromegaly. J Vet Intern Med 2012;26:757.
24. Abraham LA, Helmond SE, Mitten RW, et al. Treatment of an acromegalic cat with the dopamine agonist L-deprenyl. Aust Vet J 2002;80:479–83.
25. Slingerland LI, Voorhout G, Rijnberk A, et al. Growth hormone excess and the effect of octreotide in cats with diabetes mellitus. Domest Anim Endocrinol 2008;35(4):352–61.
26. Meij BP, Auriemma E, Grinwis G, et al. Successful treatment of acromegaly in a diabetic cat with transsphenoidal hypophysectomy. J Feline Med Surg 2010; 12:406–10.
27. Meij BP, Galac S, Kooistra H. Surgical treatment of acromegaly in cats. In: Voorjaarsdagen Proceedings Committee, editor. Proceedings of the Voorjaarsdagen. Amsterdam (The Netherlands): 2012. p. 232–3.
28. Blois SL, Holmberg DL. Cryohypophysectomy used in the treatment of a case of feline acromegaly. J Small Anim Pract 2008;49:596–600.
29. Brearley MJ, Polton GA, Littler RM, et al. Coarse fractionated radiation therapy for pituitary tumours in cats: a retrospective study of 12 cases. Vet Comp Oncol 2006;4:209–17.
30. Dunning MD, Lowrie CS, Bexfield NH, et al. Exogenous insulin treatment after hypofractionated radiotherapy in cats with diabetes mellitus and acromegaly. J Vet Intern Med 2009;23(2):243–9.
31. Niessen SJ, Powney S, Guitian J, et al. Evaluation of a quality-of-life tool for cats with diabetes mellitus. J Vet Intern Med 2010;24(5):1098–105.
32. Andrews RC, Walker BR. Glucocorticoids and insulin resistance: old hormones, new targets. Clin Sci (Lond) 1999;96:513–23.
33. Rooney DP, Neely RD, Cullen C, et al. The effect of cortisol on glucose-6-phosphate cycle activity and insulin action. Clin Endocrinol Metab 1994;77:1180–3.
34. Rizza RA, Mandarino LJ, Gerich J. Cortisol-induced insulin resistance in man: impaired suppression of glucose production and stimulation of glucose utilization due to a postreceptor defect of insulin action. J Clin Endocrinol Metab 1982;54:131–8.

35. Chavez M, Seeley RJ, Green PK, et al. Adrenalectomy increases sensitivity to central insulin. Physiol Behav 1997;62:631–4.
36. Ling ZC, Khan A, Delaunay F, et al. Increased glucocorticoid sensitivity in islet beta-cells: effects on glucose 6-phosphatase, glucose cycling and insulin release. Diabetologia 1998;41:634–9.
37. Delaunay F, Khan A, Cintra A, et al. Pancreatic beta cells are important targets for the diabetogenic effects of glucocorticoids. J Clin Invest 1997;100:2094–8.
38. Lambillotte C, Gilon P, Henquin JC. Direct glucocorticoid inhibition of insulin secretion: an in vitro study of dexamethasone effects in mouse islets. J Clin Invest 1997;99:414–23.
39. Feldman EC, Nelson RW. Hyperadrenocorticism in cats (Cushing's syndrome). In: Feldman EC, Nelson RW, editors. Canine and feline endocrinology and reproduction. St Louis (MO): Saunders; 2004. p. 358–93.
40. Nelson RW, Feldman EC, Smith MC. Hyperadrenocorticism in cats: seven cases (1978–1987). J Am Vet Med Assoc 1988;193:245–50.
41. Watson PJ, Herrtage ME. Hyperadrenocorticism in six cats. J Small Anim Pract 1998;39:175–84.
42. Rossmeisl JH Jr, Scott-Moncrieff JC, Siems J, et al. Hyperadrenocorticism and hyperprogesteronemia in a cat with an adrenocortical adenocarcinoma. J Am Anim Hosp Assoc 2000;36:512–7.
43. Blois SL, Dickie EL, Kruth SA, et al. Multiple endocrine diseases in cats: 15 cases (1997–2008). J Feline Med Surg 2010;12:637–42.
44. Spada E, Proverbio D, Giudice C, et al. Pituitary-dependent hyperadrenocorticism and generalised toxoplasmosis in a cat with neurological signs. J Feline Med Surg 2010;12:654–8.
45. Fracassi F, Mandrioli L, Diana A, et al. Pituitary macroadenoma in a cat with diabetes mellitus, hypercortisolism and neurological signs. J Vet Med A Physiol Pathol Clin Med 2007;54:359–63.
46. Meij BP, Voorhout G, van den Ingh TS, et al. Transsphenoidal hypophysectomy for treatment of pituitary-dependent hyperadrenocorticism in 7 cats. Vet Surg 2001; 30:72–86.
47. Meij BP, van der Vlugt-Meijer RH, van den Ingh TS, et al. Somatotroph and corticotroph pituitary adenoma (double adenoma) in a cat with diabetes mellitus and hyperadrenocorticism. J Comp Pathol 2004;130:209–15.
48. Schwedes CS. Mitotane (o, p'-DDD) treatment in a cat with hyperadrenocorticism. J Small Anim Pract 1997;38:520–4.
49. Boag AK, Neiger R, Church DB. Trilostane treatment of bilateral adrenal enlargement and excessive sex steroid hormone production in a cat. J Small Anim Pract 2004;45:263–6.
50. Calsyn JD, Green RA, Davis GJ, et al. Adrenal pheochromocytoma with contralateral adrenocortical adenoma in a cat. J Am Anim Hosp Assoc 2010;46(1): 36–42.
51. Roccabianca P, Rondena M, Paltrinieri S, et al. Multiple endocrine neoplasia type-I-like syndrome in two cats. Vet Pathol 2006;43(3):345–52.
52. Briscoe K, Barrs VR, Foster DF, et al. Hyperaldosteronism and hyperprogesteronism in a cat. J Feline Med Surg 2009;11(9):758–62.
53. Quante S, Sieber-Ruckstuhl N, Wilhelm S, et al. Hyperprogesteronism due to bilateral adrenal carcinomas in a cat with diabetes mellitus. Schweiz Arch Tierheilkd 2009;151(9):437–42.
54. Brown AL, Beatty JA, Lindsay SA, et al. Severe systemic hypertension in a cat with pituitary-dependent hyperadrenocorticism. J Small Anim Pract 2012;53(2):132–5.

55. Duesberg CA, Nelson RW, Feldman EC, et al. Adrenalectomy for treatment of hyperadrenocorticism in cats: 10 cases (1988-1992). J Am Vet Med Assoc 1995;207(8):1066–70.
56. Lien YH, Huang HP, Chang PH. Iatrogenic hyperadrenocorticism in 12 cats. J Am Anim Hosp Assoc 2006;42(6):414–23.
57. Roomp K, Rand J. Intensive blood glucose control is safe and effective in diabetic cats using home monitoring and treatment with glargine. J Feline Med Surg 2009;11(4):668–82.
58. Wajngot A, Giacca A, Grill V, et al. The diabetogenic effects of glucocorticoids are more pronounced in low- than in high-insulin responders. Proc Natl Acad Sci U S A 1992;89:6035–9.
59. Peterson M. Feline hyperadrenocorticism. In: Mooney CM, Peterson ME, editors. BSAVA manual of canine and feline endocrinology. Quedgeley (Gloucester): BSAVA; 2012. p. 190–8.
60. Kley S, Alt M, Zimmer C, et al. Evaluation of the low-dose dexamethasone suppression test and ultrasonographic measurements of the adrenal glands in cats with diabetes mellitus. Schweiz Arch Tierheilkd 2007;149:493–500.
61. Peterson ME, Kemppainen RJ. Comparison of intravenous and intramuscular routes of administering cosyntropin for corticotropin stimulation testing in cats. Am J Vet Res 1992;53(8):1392–5.
62. Peterson ME, Kemppainen RJ. Dose-response relation between plasma concentrations of corticotropin and cortisol after administration of incremental doses of cosyntropin for corticotropin stimulation testing in cats. Am J Vet Res 1993; 54(2):300–4.
63. Goossens MM, Meyer HP, Voorhout G, et al. Urinary excretion of glucocorticoids in the diagnosis of hyperadrenocorticism in cats. Domest Anim Endocrinol 1995; 12(4):355–62.
64. Henry CJ, Clark TP, Young DW, et al. Urine cortisol:creatinine ratio in healthy and sick cats. J Vet Intern Med 1996;10(3):123–6.
65. Cauvin AL, Witt AL, Groves E, et al. The urinary corticoid:creatinine ratio (UCCR) in healthy cats undergoing hospitalisation. J Feline Med Surg 2003;5(6):329–33.
66. De Lange MS, Galac S, Trip MR, et al. High urinary corticoid/creatinine ratios in cats with hyperthyroidism. J Vet Intern Med 2004;18(2):152–5.
67. Benchekroun G, de Fornel-Thibaud P, Dubord M, et al. Plasma ACTH precursors in cats with pituitary-dependent hyperadrenocorticism. J Vet Intern Med 2012; 26(3):575–81.
68. Zimmer C, Hörauf A, Reusch C. Ultrasonographic examination of the adrenal gland and evaluation of the hypophyseal-adrenal axis in 20 cats. J Small Anim Pract 2000;41(4):156–60.
69. Neiger R, Witt AL, Noble A, et al. Trilostane therapy for treatment of pituitary-dependent hyperadrenocorticism in 5 cats. J Vet Intern Med 2004;18(2):160–4.
70. Skelly BJ, Petrus D, Nicholls PK. Use of trilostane for the treatment of pituitary-dependent hyperadrenocorticism in a cat. J Small Anim Pract 2003;44(6): 269–72.
71. Smith RR, Mayhew PD, Berent AC. Laparoscopic adrenalectomy for management of a functional adrenal tumor in a cat. J Am Vet Med Assoc 2012;241(3): 368–72.