Insulin Resistance in Cats

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KEYWORDS

• Insulin • Diabetes mellitus • Insulin resistance
• Hyperadrenocorticism • Acromegaly

Insulin resistance is defined as decreased sensitivity to insulin. Insulin resistance is an important component of the pathogenesis of type 2 diabetes mellitus (DM), and resolution of peripheral insulin resistance in cats with type 2 DM together with good glycemic control may result in diabetic remission. In insulin-dependent diabetic cats, insulin resistance is manifested clinically as an inadequate response to an appropriate pharmacologic dose of insulin. There is no specific insulin dose that is diagnostic for insulin resistance; however most diabetic cats can be controlled on insulin doses ranging from 1 to 3 U per dose (<1 U/kg).[1–5] Cats that require insulin doses higher than 6 U per dose (>1.5 U/kg) to achieve good glycemic control, cats that have persistent hyperglycemia despite this dose of insulin, and cats with insulin needs that fluctuate or increase significantly over time should be evaluated for insulin resistance. This article focuses on the clinical problem of insulin resistance in insulin-dependent diabetic cats.

PATHOPHYSIOLOGY OF FELINE DM

DM is a common endocrine disease in cats characterized by an absolute or relative deficiency of insulin. Type 1 DM (insulin-dependent DM) is characterized by beta cell loss and minimal secretory response to β-cell secretagogues. Type 2 DM (non-insulin-dependent DM) is characterized by abnormal insulin secretion in conjunction with peripheral insulin resistance. The two types of DM are classically distinguished by response to insulin secretagogues such as glucose, glucagon, or arginine. In type 1 DM, there is decreased or negligible secretion of insulin compared with normal animals, whereas in type 2 DM, total insulin secretion may be normal or increased, with an abnormal pattern of insulin secretion. Up to 80% of diabetic cats are believed to have type 2 DM at the time of diagnosis; however, this is

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a clinical estimate only, because differentiation of the two forms of DM is clinically challenging in cats.

PATHOGENESIS OF INSULIN RESISTANCE

The causes of insulin resistance are classified depending upon whether there is interference with the availability of insulin to bind with the insulin receptor (prereceptor), interference with binding of insulin to the receptor (receptor), or factors that influence signal transduction after the interaction of insulin with the receptor (postreceptor). Receptor and postreceptor causes are difficult to distinguish and often occur concurrently. Destruction of insulin after subcutaneous administration and binding of exogenous insulin by anti-insulin antibodies are potential causes of prereceptor problems; however, these problems have been documented rarely in cats. Poor absorption of insulin from the subcutaneous site has been postulated as the cause of a poor clinical response to ultralente insulin in some cats.[1] The most common causes of insulin resistance in cats are mediated by secretion of hormones that antagonize the effects of insulin due to receptor or postreceptor causes (**Table 1**). Glucocorticoids, progestagens, catecholamines, thyroid hormones, growth hormone, and glucagon are implicated most commonly. The role of sex hormones and androgens in insulin resistance is unknown. Stress hyperglycemia mediated by catecholamines is common in cats and may mimic insulin resistance.[6]

CLINICAL INDICATORS OF INSULIN RESISTANCE

Cats with clinically significant insulin resistance typically present with signs of poor glycemic control such as persistent polyuria, polydipsia, polyphagia, weight loss, and peripheral neuropathy despite insulin doses greater than 1.5 U/kg (6 U per dose). Specifically, clinical indications of poor glycemic control are recurrence or persistence of clinical signs of diabetes mellitus; clinical signs of hypoglycemia (lethargy, disorientation, seizures); insulin dose higher than 6 U per dose or 1.5 U/kg; and recurrent ketoacidosis.

Cats with insulin resistance usually have persistent hyperglycemia on blood glucose (BG) curves and increased serum fructosamine concentrations. Conversely, if the insulin dose has been increased inappropriately or if the severity of insulin resistance fluctuates, affected cats may have clinical signs of hypoglycemia such as disorientation or seizures. Insulin resistance must be differentiated from other causes of poor glycemic control. Specifically, causes of poor glycemic control in diabetic cats include problems with owner compliance; inappropriate insulin dose or formulation; insulin-induced hypoglycemia (Symogi effect); rapid metabolism of insulin; and insulin resistance.

Other differential diagnoses usually can be excluded by the history and evaluation of a BG curve.

CAUSES OF INSULIN RESISTANCE IN CATS

There are currently no published prospective or retrospective studies specifically evaluating the causes of insulin resistance in cats. Common concurrent diseases identified in cats with DM or diabetic ketoacidosis include pancreatitis, hepatic lipidosis, cholangiohepatitis, urinary tract infection, renal failure, hyperthyroidism, inflammatory bowel disease, acromegaly, and heart disease.[7–14] Treatment with exogenous glucocorticoids or progestagens is also a common historical finding. Clinical experience suggests that these concurrent problems also cause insulin resistance in cats

Table 1
Proposed mechanisms of hormone-mediated insulin resistance in cats

Hormone	Proposed Mechanism(s) of Insulin Resistance	Associated Disease States
Glucocorticoids	Increased hepatic gluconeogenesis Decreased tissue use of glucose Decreased receptor affinity for insulin Decreased number and affinity of glucose transporters Increased glucagon and free fatty acid concentrations	Stress Hyperadrenocorticism Exogenous administration
Progesterone, progestagens	Reduced insulin binding Reduced glucose transport in tissues	Diestrus/pregnancy Exogenous administration (eg, megestrol acetate) Progestagen-secreting adrenal tumors
Growth hormone	Decreased number of insulin receptors Inhibition of glucose transport Decreased glucose use Increased glucose production Postinsulin receptor defect in peripheral tissues Increased lipolysis	Acromegaly
Glucagon	Activation hepatic glycogenolysis Increased hepatic glucose production	Bacterial infection Pancreatitis Trauma Congestive heart failure Renal failure Glucagonoma
Thyroid hormones	Decreased insulin synthesis and secretion Impaired insulin receptor binding Postreceptor defect Disproportionate increase in proinsulin secretion	Hyperthyroidism
Epinephrine	Stimulation of hepatic and renal glucose production Decreased glucose use Decreased insulin secretion Stimulation of glucagon secretion Mobilization of gluconeogenic precursors	Stress Pheochromocytoma

(**Box 1**). In a study of 104 cats with DM, glycemic regulation was worse in 21 cats with concurrent disease than in 33 cats without concurrent disease.[11] The severity of insulin resistance varies with the underlying disease. In some disorders, the resistance can be overcome by increasing the dose or changing the insulin formulation to a more potent product. In other diseases such as acromegaly, insulin resistance is severe and cannot be overcome by even extremely large insulin doses.[14,15] Disorders such as chronic pancreatitis often cause fluctuating insulin resistance. The insulin requirement in these cases fluctuates with time and increasing the insulin dose may lead to intermittent hypoglycemia.

Obesity

Obesity causes insulin resistance in cats and is important in the pathogenesis of DM in cats. Obesity occurs when energy intake exceeds energy output, and risk factors in cats include excessive food intake, indoor confinement, and physical inactivity.[16] Insulin sensitivity decreases by more than 50% in obese compared with healthy weight cats.[17] Insulin resistance associated with obesity in diabetic cats is typically mild and reversible and can be overcome by relatively small increases in insulin dose. In addition, cats with poor glycemic control undergo significant weight loss, so obesity alone is rarely a cause of severe insulin resistance. Acromegalic cats usually have a stable weight or gain weight despite poor glycemic control, so acromegaly should be considered in obese cats with profound insulin resistance.

Exogenous Glucocorticoids or Progestagens

Exogenous glucocorticoids and progestagens such as megestrol acetate cause insulin resistance (see **Table 1**). Administration of these drugs has been identified as an important precipitating factor for DM in cats.[9,11] Use of these drugs in an established diabetic cat may cause clinically significant insulin resistance and should be

Box 1
Causes of insulin resistance in cats

- Drug administration (progestagens/corticosteroids)
- Infection (urinary tract/oral cavity/sepsis)
- Hyperthyroidism
- Acromegaly
- Pancreatitis
- Renal disease
- Hepatic disease
- Cardiac insufficiency
- Hyperlipidemia
- Neoplasia
- Severe obesity
- Exocrine pancreatic insufficiency
- Hyperadrenocorticism
- Pheochromocytoma

avoided. In cats with DM that require treatment with either glucocorticoids or progestagens for concurrent disease, the dose should be reduced to the minimum that will control the disease process, and the insulin dose should be increased cautiously to control hyperglycemia.

Pancreatitis

Pancreatitis is a common and frustrating problem in cats and may contribute to the pathogenesis of feline DM. Pancreatitis is also a common concurrent disease in diabetic cats and an important cause of insulin resistance. In a report of 37 diabetic cats that underwent necropsy, acute or subacute pancreatitis was identified in 2 cats; chronic pancreatitis was identified in 17 cats, and pancreatic neoplasia was identified in 8 cats.[11] Chronic inflammation due to pancreatitis causes insulin resistance that may impair glycemic regulation (see **Table 1**). In a study of 104 cats with DM, there was a trend for poorer glycemic control in cats with pancreatitis compared with those without.[11] Compounding the problem of insulin resistance in cats with pancreatitis is the cyclic nature of the disease. Because both insulin demands and appetite fluctuate with the severity of inflammation, clinical signs of poor glycemic control often coexist with an increased risk of clinical hypoglycemia.

Diagnosis of pancreatitis relies on evaluation of clinical signs; physical examination; abdominal ultrasound; and measurement of serum lipase, feline trypsin-like immunoreactivity, or feline pancreatic lipase immunoreactivity.[18] Unfortunately, in some cats it may be difficult to confirm a diagnosis without resorting to exploratory laparotomy and histopathology. Treatment of chronic pancreatitis in cats relies on use of intravenous fluid therapy, nutritional support, antiemetics, analgesia, and sometimes-cautious use of glucocorticoids. In general, the long-term prognosis for resolution of pancreatic inflammation is guarded.

Bacterial Infection

Bacterial infection is an important cause of insulin resistance in diabetic patients (see **Table 1**). Hyperglucagonemia has been implicated as the cause of insulin resistance in people with bacterial infection, but this has yet to be documented in the cat. Cats with DM are at increased risk of bacterial infection, especially of the urinary tract. Decreased urine concentration and glucosuria increase the likelihood of bacterial proliferation within the urinary tract. In a study of 141 diabetic cats that underwent urine collection by cystocentesis, urinary tract infection was identified in 13% of cats.[12] Only 40% of the cats with urinary tract infections exhibited clinical signs. Other studies also have documented that bacterial infections are common concurrent diseases in diabetic cats.[7,11] Other common sites of bacterial infection include the oral cavity, the skin, and the biliary tract. Other factors that have been hypothesized to increase the risk of infection in patients with DM include impaired humoral and cell-mediated immunity, abnormal neutrophil chemotaxis, and defects in phagocytosis and intracellular killing of bacteria.[1]

Renal Disease

Renal disease is common in diabetic cats. and glomerulosclerosis is the most common histopathologic finding.[9,11] Renal insufficiency may occur secondary to DM (diabetic nephropathy) or be a concurrent disorder. Moderate to severe renal failure may cause insulin resistance; however, cats also may be at increased risk for hypoglycemia because of decreased renal clearance of insulin.[1] Thus patients with concurrent renal failure and DM may be frustrating to manage. Problems with glycemic regulation may be compounded by anorexia. Polyuria and polydipsia caused by

renal failure make the assessment of glycemic regulation more challenging. Diagnosis of renal disease relies on evaluation of physical examination findings and review of the minimum database (complete blood cell count [CBC], serum chemistry profile, urinalysis). Diagnostic tests that are helpful in further evaluating the cause of renal dysfunction in diabetic cats include urine culture, measurement of urine protein:creatinine ratio, and ultrasound examination of the urinary tract.

Hyperthyroidism

Hyperthyroidism has been reported to cause insulin resistance in both experimental and naturally occurring hyperthyroidism. Hyperthyroid cats have normal resting BG and insulin concentrations but have abnormal glucose tolerance.[19,20] Surprisingly, insulin resistance in spontaneous hyperthyroidism did not resolve after resolution of hyperthyroidism, possibly because of the influence of obesity.[20] Because both DM and hyperthyroidism are common disorders in geriatric cats, evaluation of thyroid status should be included in the minimum database of all geriatric diabetic cats. The diagnosis of hyperthyroidism is usually straightforward and is based on history, physical examination, and documentation of increased serum concentration of total T4. Confirming a diagnosis of hyperthyroidism may be more challenging in cats with severe systemic illness because of the effect of concurrent disease on resting thyroid hormone concentrations.[21] Additional diagnostic tests that may be necessary in such cats include measurement of free T4, a T3 suppression test, or scintigraphy.

Heart Disease

Heart disease also may cause insulin resistance and predisposition to ketoacidosis in diabetic cats. In a retrospective study of 20 diabetic cats and 57 control cats in a primary care practice, cats with DM were 10 times more likely to die of heart failure than control cats.[10] Occult heart disease should be considered in any diabetic cat with unexplained insulin resistance. Diagnosis is made by evaluation of the history and physical examination, thoracic radiography, electrocardiography, and echocardiography.

Neoplasia

Underlying nonendocrine neoplasia such as lymphoma or mast cell tumor are also common concurrent disorders in diabetic cats and may contribute to insulin resistance.[7–9] The diagnosis usually is made by evaluation of the history, physical examination, clinicopathologic abnormalities, results of diagnostic imaging, and histopathology. Bone marrow aspiration and more advanced imaging may be required in some cases.

Acromegaly

Acromegaly is caused by excess secretion of growth hormone from a pituitary adenoma.[22–24] Excess circulating growth hormone (GH) causes insulin resistance, carbohydrate intolerance, hyperglycemia and DM (see **Table 1**). Excess GH results in increased secretion of insulin growth factor 1 (IGF-1) from the liver and peripheral tissues. The anabolic effects of IGF-1 cause proliferation of bone, cartilage, and soft tissues, with resultant organomegaly. Although feline acromegaly in the past was considered a rare disorder, recent studies suggest that it may be a more common cause of insulin resistance in diabetic cats than previously was recognized.[14,15,24] In a study of 184 diabetic cats with a wide range of glycemic control, 32% of cats had markedly increased IGF-1 concentrations, and acromegaly was confirmed in 17 of these cats.[14]

Most cats with acromegaly are middle-aged or older (median 10 years of age, range 4 to 17 years), and 90% are male (intact or castrated).[14,15,22–24] All reported cases to date have had DM at the time of diagnosis. Clinical signs include evidence of poor glycemic control (polyuria, polydipsia, and polyphagia), large body size, weight gain despite poor glycemic control, and enlargement of the head and extremities (**Fig. 1**). Respiratory stridor is reported in up to 53% of acromegalic cats and is caused by enlargement of the tongue and oropharyngeal tissues.[14] Acromegalic cats tolerate high doses of insulin. Median insulin dose in one group of 17 acromegalic cats was 7 U every 12 hours (range 2 to 35 U), and in another group of 19 acromegalic cats, the dose was 1.9 U/kg (range 1.1 to 4.3).[14,15] Physical examination may reveal abdominal organomegaly, inferior prognathia, cataracts, clubbed paws, broad facial features, widened interdental spaces, cardiac murmurs or arrhythmias, respiratory stridor, lameness, peripheral neuropathy, and central neurologic signs attributable to an enlarging pituitary mass (**Fig. 2**). Cardiomegaly and renomegaly may be evident on imaging studies. Although weight loss caused by poorly regulated DM may occur initially, a key finding in acromegalic cats is weight gain or a stable weight (lack of weight loss) in a diabetic cat that by all other indications has poor glycemic control. Many acromegalic cats have a high body weight (range 3.5 to 9 kg), but as a group the body weights of acromegalic cats are not significantly greater than those of diabetic cats without acromegaly.[14,15]

Some cats with acromegaly may be phenotypically indistinguishable from normal cats. Acromegaly therefore should be considered in the differential diagnosis of any cat with insulin resistance if other more common causes have been ruled out, especially if the body weight is stable to increasing. Some clinicians have recommended evaluation for acromegaly in any cat that does not go into diabetic remission with appropriate diet and insulin therapy.[24]

A tentative diagnosis of acromegaly is made by measurement of GH and IGF-1 concentrations, and assays for both IGF-1 and GH have been validated in the cat.[14,25–27] Measurement of IGF-1 is a good screening test for acromegaly and has a specificity of 92% and sensitivity of 84% in diabetic cats with insulin resistance.[15] IGF-1 concentrations may be low in untreated diabetic cats, while some poorly controlled diabetic cats have slightly increased IGF-1 concentrations.[25,27] GH concentration is increased in most acromegalic cats.[26] GH has a short half-life and is episodically secreted; this is likely why there is some overlap in GH concentrations with nonacromegalic diabetic cats.[27] Ideally, both IGF-1 and GH concentration should

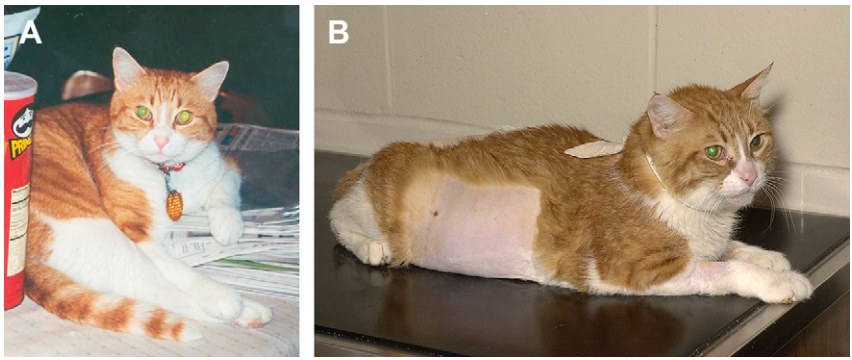

Fig. 1. Photograph of a 10-year-old male castrated cat three years before (*A*) and at time of diagnosis of (*B*) diagnosis of acromegaly.

Fig. 2. Photograph of an 11-year male domestic short hair (DSH) cat with acromegaly demonstrating enlargement of the head and mild prognathia inferior.

be measured in a cat with suspected acromegaly. Imaging of the brain should be performed to confirm the diagnosis.[14,15] In most acromegalic cats, a pituitary tumor can be identified by either computed tomography (CT) or magnetic resonance imaging (MRI) (**Fig. 3**). In one case of confirmed acromegaly, acidophil proliferation within the pituitary gland did not result in a detectable mass on CT or MRI.[14] Thus even negative MRI findings do not preclude a diagnosis of acromegaly.

Radiation therapy is the most effective treatment for feline acromegaly. Radiation therapy has been reported to result in improvement of neurologic signs and decreased insulin requirements or diabetic remission in cats with acromegaly.[28–31] Interestingly, IGF concentrations do not decrease in concert with the clinical response.[30] Median survival in 14 cats treated with radiation therapy was 28 months.[30] Unfortunately, the cost and availability of radiation therapy often limit access to treatment.

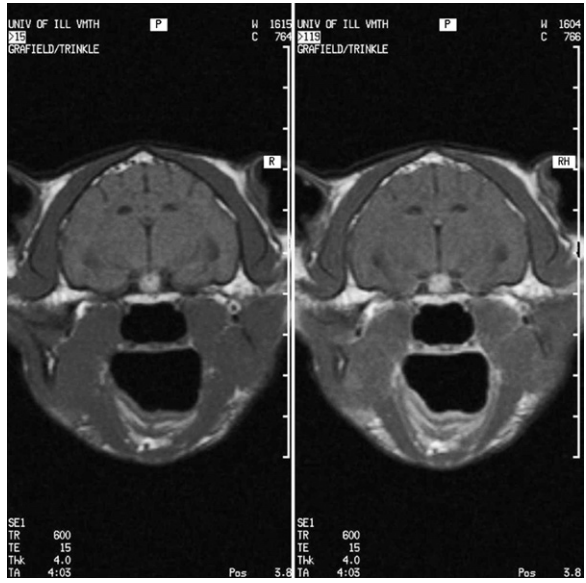

Fig. 3. MRI study demonstrating a pituitary mass in a cat with acromegaly.

Hypophysectomy has not been evaluated extensively in the treatment of feline acromegaly, although trans-sphenoidal cryohypophysectomy was used successfully to treat one acromegalic cat.[32] Neither octreotide nor L-deprenyl has been effective in amelioration of clinical signs of acromegaly in cats. In cats in which radiation therapy is not possible because of financial or logistical concerns, long-term survival may be achieved in acromegalic cats if DM is managed with high doses of insulin. Because of the profound insulin resistance associated with acromegaly, hypoglycemic complications using this approach are unusual. A median survival time of 20 months was reported in a group of 14 acromegalic cats, of which only 2 were treated with radiation and octreotide.[23] Cause of death in these cats was most commonly due to renal failure or congestive heart failure or a combination.[23]

Hyperadrenocorticism

Hyperadrenocorticism (HAC) is also an important cause of insulin resistance in cats. HAC is caused by excess secretion of adrenocortical hormones from either a functional pituitary tumor (PDH) or a functional tumor of the adrenal cortex. Cortisol is the most common hormone secreted in HAC; however, other adrenal hormones such as androstenedione, progesterone, 17- hydroxyprogesterone, estradiol, aldosterone and testosterone also may be secreted in cats with functional adrenocortical tumors. Eighty-five percent of cats with HAC have PDH, while 15% are diagnosed with functional adrenocortical tumors. Approximately 80% of cats with HAC are diabetic at the time of diagnosis.

Cats with HAC are middle aged to older (median 10 years of age, range 5 to 16 years), and females are slightly over-represented.[1,33–35] Clinical signs include evidence of poor glycemic control (polyuria, polydipsia, polyphagia, weight loss, and peripheral neuropathy), lethargy, abdominal enlargement or a pot-bellied appearance, muscle atrophy, unkempt hair coat, bilaterally symmetric alopecia, cutaneous fragility, and recurrent abscess formation (**Fig. 4**). Cats with HAC are predisposed to bacterial infection, so clinical signs of urinary tract infection, pyoderma and respiratory tract infection also may be present. Physical examination may reveal hepatomegaly, seborrhea, thinning of the skin, and cutaneous lacerations in addition to the clinical signs already discussed. Skin fragility may be so severe that tearing of the skin occurs during routine grooming of the hair coat (**Fig. 5**). Virilization caused by excess sex hormone secretion and hyperaldosteronism also have been reported in cats with HAC.[36,37] The results of a CBC, biochemical panel, and urinalysis are usually consistent with the presence of DM. Increased alkaline phosphatase, alanine transferase, hypercholesterolemia, hyperglycemia, and low serum urea nitrogen (BUN) are common. Cats do not have a steroid-induced isoenzyme of alkaline phosphatase, so changes in this enzyme are less prominent than seen in dogs, and increases likely are caused by poorly regulated DM. Endocrine tests used to confirm the diagnosis include the corticotropin (ACTH) stimulation test, the low-dose dexamethasone suppression test, and the urine cortisol:creatinine ratio (C:Cr). The urine cortisol:creatinine ratio is a useful screening test for hyperadrenocorticism.[38–41] Urine for measurement of the C:Cr ratio should be collected at home to minimize the influence of stress. If the C:Cr ratio is normal, HAC is unlikely; however, increases also may occur in cats with other concurrent illness, so additional testing is necessary for confirmation.[38] The low-dose dexamethasone suppression test is performed using a higher dose of dexamethasone (0.1 mg/kg intravenously) than in the dog. A baseline blood sample is collected, and additional samples are collected at 4 and 8 hours after dexamethasone administration. Serum cortisol concentration is suppressed (<1.5 μg/dL, <40 mmol/L) at 8 hours in normal cats but not in cats with HAC. A few cats with HAC will have

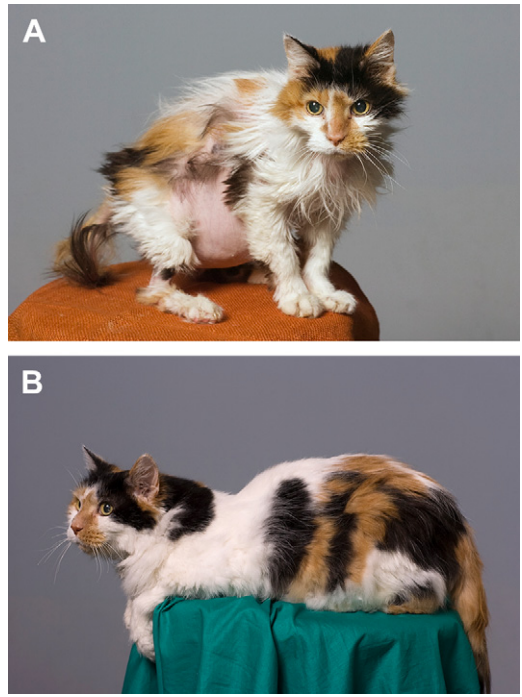

Fig. 4. (*A*) Photograph of a 14-year-old female spayed domestic long haired cat with pituitary-dependent hyperadrenocorticism. Note the unkempt hair coat, alopecia, muscle atrophy, and pot-bellied appearance. (*B*) Same cat after 6 months of treatment with trilostane at a dose of 25 mg by mouth every 12 hours.

a normal result with this dose of dexamethasone. If the index of suspicion for HAC is high, a second test using the lower dose of dexamethasone (0.01 mg/kg) can be performed. Interpretation is difficult, however, because serum cortisol concentrations in some normal cats will not be suppressed at this dose. The ACTH stimulation test is not a particularly sensitive or specific test in cats, but it is useful in cases in which dexamethasone suppression testing is difficult to interpret and in cats with suspected

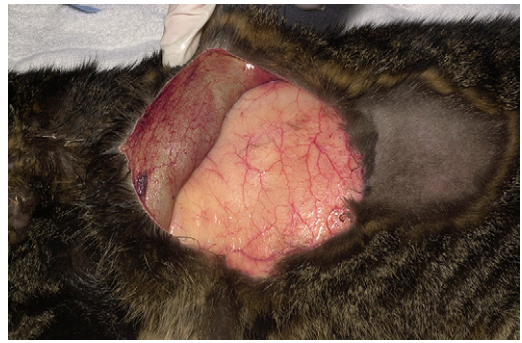

Fig. 5. Photograph of a severe self induced cutaneous laceration (after grooming) in a 12-year-old female spayed cat with hyperadrenocorticism.

iatrogenic HAC.[1] The ACTH stimulation test is performed using a dose of 125 μg of Cortrosyn administered intravenously or intramuscularly. Samples should be collected at baseline, and at 30 and 60 minutes after IM administration of ACTH, or 60 and 90 minutes after intravenous administration.[42] A post-ACTH serum cortisol concentration greater than 150 μg/dL (413 nmol/L) in a cat with clinical signs consistent is supportive of a diagnosis of HAC.[1,35,43]

Some adrenal carcinomas in cats have been associated with high circulating concentrations of other adrenal hormones such as androstenedione, progesterone, 17- hydroxyprogesterone estradiol, testosterone, and aldosterone (**Fig. 6**).[36,37,44,45] Cortisol concentrations in these cases are typically low, with little response to ACTH stimulation. A sex hormone-secreting tumor should be suspected in cats with clinical signs of HAC, an adrenal mass detected by ultrasound, and a blunted cortisol response to ACTH. All cats reported to date with sex hormone-secreting adrenal tumors have had adrenocortical carcinomas. Confirmation is by a sex hormone profile with hormones measured before and after ACTH stimulation testing.

Tests that are helpful for differentiation of pituitary-dependent from adrenal-dependent hyperadrenocorticism in cats include the high-dose dexamethasone suppression test (0.1 mg/kg or 1 mg/kg intravenously), endogenous ACTH stimulation, and abdominal ultrasonography.[1,41] Unfortunately, there is little published information comparing the diagnostic performance of these tests in cats. Clinical experience suggests that

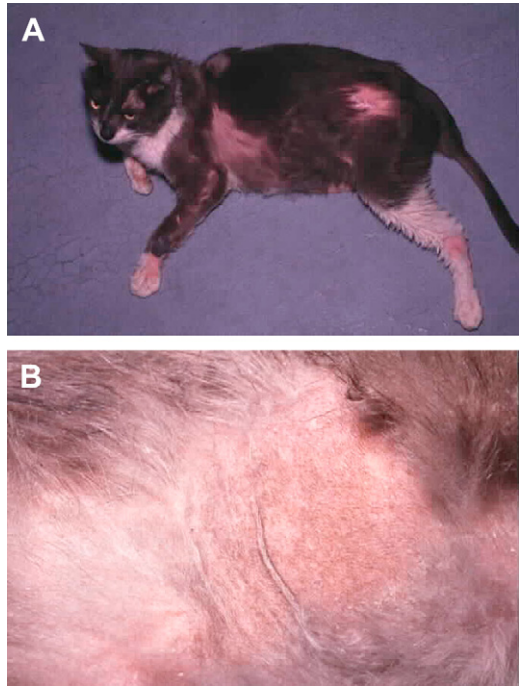

Fig. 6. (*A*) Photograph of a 7-year-old male castrated DSH cat with a sex hormone-secreting adrenal tumor. Note the unkempt hair coat and the areas of alopecia at the locations of previous cutaneous laceration. (*B*) Close-up view of the skin in the same cat showing severe thinning of the skin.

measurement of endogenous ACTH and adrenal ultrasonography are the most reliable differentiating tests.[41,46]

Treatment options for cats with HAC depend upon whether the disease is pituitary-dependent or adrenal-dependent. Adrenalectomy is the treatment of choice in cats with adrenal tumors.[34] In cats with PDH, bilateral adrenalectomy also has resulted in a successful outcome (**Fig. 7**).[34] The most successful drug for medical treatment of feline HAC is trilostane, but not all cats respond well to treatment.[43] The dose range of trilostane that has been reported to be effective in cats with PDH is 15 mg by mouth every 24 hours to 60 mg by mouth every 12 hours (**Fig. 8**).[37,43,47] Other drugs that have been used with limited success in cats with HAC include mitotane, metyrapone, and aminoglutethimide.[45,48–50] Other options in cats with PDH include hypophysectomy or radiation therapy.[28,29,41]

DIAGNOSTIC APPROACH TO INSULIN RESISTANCE IN CATS

Clinical Evaluation of Cats with Suspected Insulin Resistance

Assessment of cats with suspected insulin resistance requires performance of a BG curve, which should allow the clinician to rule out other causes of poor response to insulin (see **Box 1**). In cats receiving twice-daily insulin, a 12-hour BG curve is usually adequate. It is important to take into consideration the level of stress of the patient when interpreting the results of BG curves. It is also important to appreciate that BG curves show significant day-to-day variability.[51] Other measures such as clinical signs, results of urine and BG measurements at home, serum fructosamine concentrations, and changes in physical examination (especially body weight), should be taken into account when interpreting the results. Typically a BG curve in a cat with insulin resistance shows persistently high BG concentrations with no detectable nadir after insulin administration (see **Fig. 8**). Measurement of serum fructosamine is also useful in evaluation of cats with suspected insulin resistance. In cats with true insulin resistance, the fructosamine concentration is usually high, suggestive of poor glycemic control (**Table 2**). In cats with suspected insulin resistance in which fructosamine concentrations are consistent with good or moderate control, other causes of poor glycemic control should be considered. If the serum fructosamine concentration is low or in the reference range for a normal cat, insulin-induced hypoglycemia is the most likely cause of poor glycemic control.

The underlying cause of insulin resistance in cats usually can be identified by evaluation of historical findings, physical examination (including thorough oral

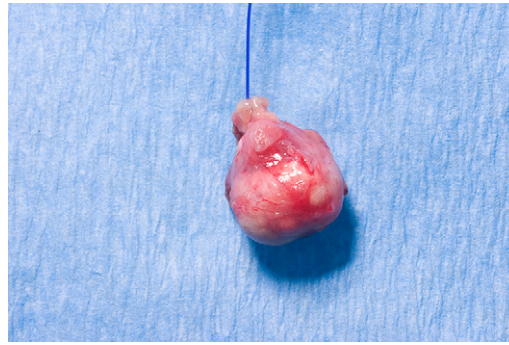

Fig. 7. Photograph of an adrenocortical carcinoma removed from a cat with signs of feminization caused by excess estradiol secretion from the tumor.

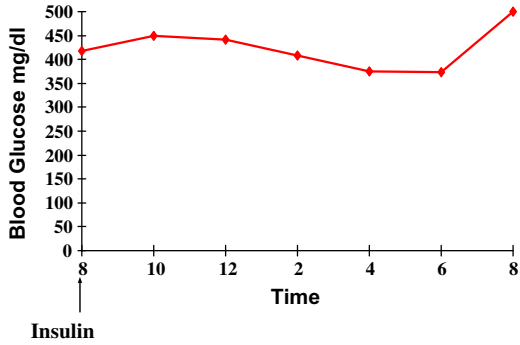

Fig. 8. Typical blood glucose curve in a cat with insulin resistance caused by acromegaly. Note the persistent increase in blood glucose and lack of a detectable nadir.

examination), and minimum database (CBC, biochemical profile, urinalysis, total T4) in addition to routine diagnostic tests such as urine culture, thoracic radiographs, abdominal ultrasound, and feline pancreatic enzyme assays. If this testing is unrewarding, the clinician should consider testing for concurrent endocrine disorders such as hyperadrenocorticism and acromegaly. The incidence of acromegaly in cats with severe insulin resistance appears to be higher than previously suspected, so in some cats it may be more appropriate to screen for acromegaly early in the work-up.[13,52] Clinical findings that would lead the clinician to be suspicious of acromegaly include absence of evidence of other underlying disease such as pancreatitis, heart disease, renal failure or hyperadrenocorticism, and a stable weight with no evidence of recurrent ketoacidosis (**Table 3**). Clinical signs that increase the index of suspicion for HAC include dermatologic signs, a pot-bellied appearance, persistent weight loss, and muscle atrophy. Adrenomegaly may be identified on abdominal ultrasound in cats with HAC, but because of the anabolic effects of IGF-1, cats with acromegaly also may have enlarged adrenal glands.

If no cause of insulin resistance can be identified in a cat with insulin resistance, strategies that may be useful for management of affected cats include an empiric change in diet or insulin formulation, attempts to control body weight in obese cats, and careful increases in insulin dose in cats with severe persistent insulin resistance. In cats with fluctuating insulin requirements, this approach may not be possible without risk of hypoglycemia. If no improvement in insulin sensitivity is observed, reevaluation is recommended in 2 to 3 months. In some cases, disease progression over time may make detection of underlying disease easier.

Table 2
Fructosamine concentrations in diabetic cats

	Fructosamine Concentration (μmol/L)
Normal	142–450
Good control	<500
Fair control	500–614
Poor control	>614

Table 3
Comparison of clinical features of feline hyperadrenocorticism and acromegaly

	Acromegaly	Hyperadrenocorticism
Age	Median 10 years of age, range 4–17 years	Median 10 years of age, range 5–16 years
Sex	90% male	60% female
Body weight	Usually weight gain or stable weight but may also be loss of weight caused by poorly regulated DM	Weight loss is typical
Skin	No skin hair coat changes	Unkempt hair coat, alopecia, dermal and epidermal atrophy, cutaneous lacerations
Adrenal size	Normal to increased	Usually increased (either unilateral or bilateral)
Body size	Often larger cats affected, but cats may also be normal size	Body size is normal
Muscle mass	Normal muscle mass	Muscle atrophy common
Abdominal and thoracic organs	Renomegaly Hepatomegaly Cardiomegaly	Normal except for adrenals
Joints	Arthopathy	Normal
Predisposition to infection	Slightly predisposed because of DM	Marked increase in urinary tract infections, respiratory infections, and abscesses caused by both HAC and DM

SUMMARY

Most cats with true insulin resistance have underlying concurrent disease. The most common causes of insulin resistance are pancreatitis and bacterial infection. Acromegaly and HAC are important causes of insulin resistance in cats, and acromegaly may currently be underdiagnosed. Recent advances in definitive treatment of acromegaly and HAC may improve the quality of life and long-term survival of affected cats.

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