

Endocrinology

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ENDOCRINE PANCREATIC DISORDERS

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OVERVIEW

The endocrine pancreas comprises multitudes of islands of cells within the exocrine pancreas known as the *islets of Langerhans*. The islets represent only 2% of the pancreas and comprise several types of cell. Each cell type secretes a different hormone. The major cell types and the hormones they produce are found in Table 24-1. The close interrelationship among these different cell types allows for direct control of secretion of some hormones by other hormones. For example, insulin inhibits glucagon secretion and somatostatin inhibits the secretion of both insulin and glucagon. Activity of beta cells and production of insulin are of main importance for diabetes mellitus (DM).²⁴

DIABETES MELLITUS

Epidemiology

The prevalence of feline DM is in the order of 1 in 100 to 1 in 200 cases, with higher numbers of cases seen in referral practice than in first opinion practice.^{5,62,93,95} The number of diabetes cases in cats appears to be increasing (Figure 24-1), and this may relate to higher obesity rates and more cats being fed high-carbohydrate diets.⁹³ Male cats appear to be at greater risk, representing approximately 60% to 70% of all diabetics.^{5,62,89,93,95} Increasing age also correlates with increasing risk of DM, with approximately 20% to 30% of diabetics diagnosed at 7 to 10 years of age and 55% to 65% of diabetics diagnosed when older than 10 years of age.^{5,89,93,95} Numerous studies have indicated that Burmese are at higher risk of diabetes than other cats in Australia and New Zealand,^{5,62,95,114,121} and a United Kingdom survey has indicated likewise.⁷⁷ This does not appear to be the case in North America,

where the Burmese breed appears to be genetically distinct. One North American study indicated an overrepresentation of Siamese cats,⁸⁹ but a subsequent study did not confirm this.⁹³

Clinical Signs and Diagnosis

According to one authority, "Currently, there are no internationally accepted criteria for the diagnosis of diabetes in cats."⁹⁴ Despite this statement, DM is usually recognized as persistent hyperglycemia above the renal threshold for normal cats, which is blood glucose (BG) greater than 16 mmol/L (288 mg/dL), with consistent clinical signs (polyuria, polydipsia, and weight loss). Elevations of BG above the renal threshold result in glycosuria. Caution must be taken to rule out stress hyperglycemia (reportedly as high as 60.4 mmol/L [1087 mg/dL]).⁵⁹ In many cases serum fructosamine concentration will be normal with stress hyperglycemia. Ruling out stress hyperglycemia can also be achieved by treating underlying conditions and then rechecking blood and urine glucose on a subsequent day. This is particularly

important if the BG is less than 20 mmol/L (360 mg/dL), intercurrent disease is present that could cause stress hyperglycemia, or typical clinical signs of DM are absent. A second test is not usually required if BG is greater than 20 mmol/L (360 mg/dL).

Evidence of gluconeogenesis (ketosis or ketonuria) supports a diagnosis of DM.⁹⁴ All diabetic cats in a recent study had at least some elevation of the plasma ketone, beta-hydroxybutyrate. Using a plasma value of 0.22 mmol/L beta-hydroxybutyrate as the cutoff value for diagnosis of DM gave a false positive rate of 9%, whereas 0.58 mmol/L reduced the false positive rate to 1.2%. No cat with moderate or severe stress-related hyperglycemia had beta-hydroxybutyrate concentrations above 0.22 mmol/L.¹³²

Fructosamine is the term used to describe glycated plasma proteins, and serum concentration of fructosamine is related to BG concentration. Serum fructosamine concentration may be used to aid the diagnosis of DM, but care must be taken because in cats a single serum fructosamine concentration measurement most likely reflects the mean BG concentration for approximately the past week (compared with longer durations in other species). Further, serum fructosamine may not exceed the reference range in cats with moderate hyperglycemia of less than 17 mmol/L (306 mg/dL),⁶⁴ making serial BG testing a more reliable indicator of diabetes. Most cats with newly diagnosed DM will have serum fructosamine levels higher than 400 µmol/L.¹⁶

Other serum or plasma biochemistry changes in DM are variable but commonly include elevations in the hepatic enzymes, alanine aminotransferase (ALT), and alkaline phosphatase (ALP). These values return to normal on successful treatment of diabetes.

Hematology is typically normal but a stress leukogram of mild neutrophilia and lymphopenia may be recognized. Concurrent infection resulting in a more pronounced neutrophilia, perhaps with a left shift, can

TABLE 24-1 The Major Cell Types of the Endocrine Pancreas and the Hormones They Produce

Cell Type	Hormone
Alpha cells (20%-25% of each islet)	Glucagon
Beta cells (60%-80% of each islet)	Insulin
Delta cells (10% of each islet)	Somatostatin
Gamma cells have two subtypes: PP (or F) cells	Pancreatic polypeptide
D cells	Vasoactive intestinal peptide
EE (or enterochromaffin) cells	Serotonin, motilin, substance P

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FIGURE 24-1 Hospital prevalence of feline diabetes mellitus. Veterinary Medical Data Base, 1970-1999. (From Prahl A, Guptill L, Glickman NW et al: Time trends and risk factors for diabetes mellitus in cats presented to veterinary teaching hospitals, J Feline Med Surg 9:351, 2007.)

be present, and successful management of diabetes requires treatment of underlying infection.

Glycosuria should be considered as part of the diagnostic criteria because this arises as a result of BG above the renal threshold. Urine may be dilute and associated with polydipsia but not necessarily so as some affected cats have concentrated urine. One study showed that 13% of cats with DM had urinary tract infection (UTI),⁴ and as with other infections, UTI must be treated to aid diabetic control.

Pathophysiology

Successful management of DM requires an understanding of its pathophysiology. Hyperglycemia resulting in DM comprises three processes:

1. Lack of insulin production
2. Lack of insulin receptivity (insulin resistance)
3. Hepatic gluconeogenesis

In the healthy individual, for most organs, insulin must bind to insulin receptors at the periphery of cells to allow entry of glucose from the bloodstream into the cell. When insulin binds to the receptor, intracellular mechanisms are activated that result in glucose transporters (contained within intracellular vesicles) moving to the cell membrane. At least 12 glucose transporter proteins (GLUTs) have been described. GLUT4 is responsible for insulin-mediated glucose uptake. GLUT4 vesicles dock on the cell membrane, and then GLUT4 fuses to the cell membrane to allow intracellular diffusion of glucose. This is a complex process mediated by at least three genes in all mammals. Glucose in the bloodstream is mostly from metabolized food.⁶³ These processes have been simplified, as depicted in Figure 24-2. There are two major organs with important differences in glucose metabolism:

1. The liver has enhanced uptake of glucose that is mediated as described previously but also stores glucose in the form of glycogen. In most species hepatic glycogen is split back into glucose (gluconeogenesis) in times of fasting, such as between meals. In cats gluconeogenesis is reported to be active even in the fed state.³⁸ Cats have low levels of glucokinase, an enzyme that facilitates conversion of glucose to glucose 6-phosphate, but high levels of glucose 6-phosphate. Glucose 6-phosphate plays a vital role in glycogen production and glycolysis (energy production).⁴³ The full implications of these feline-specific differences are not yet understood but may prove vital in our evolving understanding of the pathogenesis of feline diabetes.
2. Brain cells are permeable to glucose and can use glucose without the intermediation of insulin. The brain normally uses only glucose for energy and can

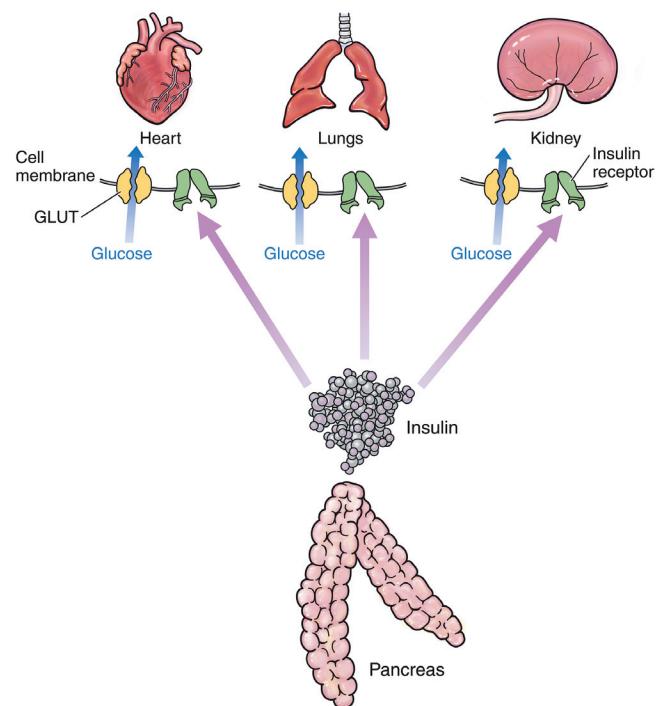


FIGURE 24-2 Normal physiology of glucose metabolism; beta islet cells of pancreas produce and secrete insulin, insulin binds to insulin receptors at cells of organs around body (e.g., heart, lungs, kidney), which increases the number of plasma membrane glucose transporters (GLUTs). GLUTs enable glucose uptake by cells.

use other substrates (e.g., fat) for energy only with difficulty (as opposed to other organs). For these reasons it is essential that BG concentration does not fall too low because hypoglycemic shock can result.³⁸

With insulin deficiency or lack of insulin receptivity, cells become deprived of glucose; glucose remains in the bloodstream; and, once the renal threshold is reached, glucose spills into the urine. Because cells are deprived of glucose, negative feedback from the cells drives appetite, resulting in polyphagia, but insofar as there is reduced cellular metabolism, concurrent weight loss also results. Weight loss is also contributed to by muscle and protein catabolism to provide substrates for gluconeogenesis. Glycosuria results in osmotic loss of water from the kidneys, so polyuria occurs. To maintain hydration the animal has a compensatory polydipsia. Because there is less cellular recognition of glucose, another negative feedback mechanism stimulates gluconeogenesis in the liver. Ketones are a by-product of gluconeogenesis, and there is a resultant increase in ketone concentrations in the blood and urine. However, ketones can create nausea and, paradoxically, make the animal inappetent.

Type 1 DM is due to lack of insulin (Figure 24-3). It is rarely described in cats. It is most often associated with

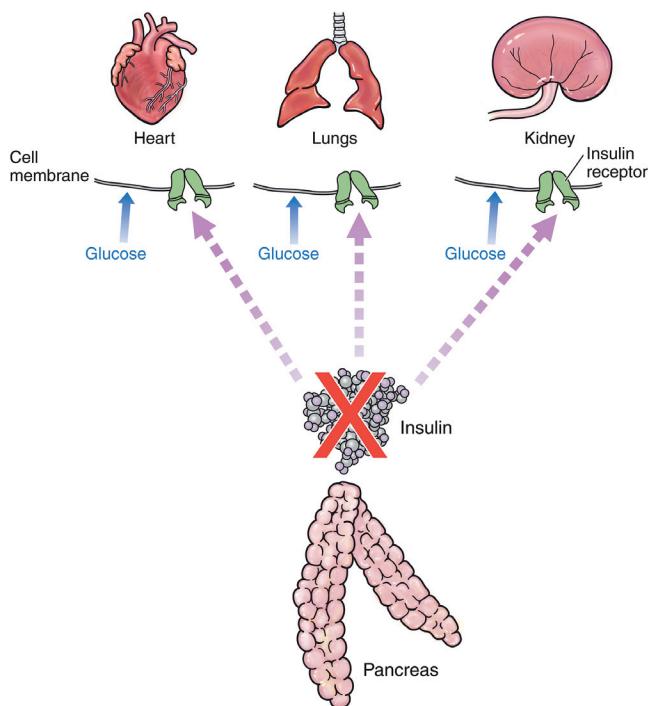


FIGURE 24-3 Type 1 diabetes mellitus, rarely described in cats; lack of production of insulin results in reduced number of plasma membrane glucose transporters (GLUTs). Fewer GLUTs means that glucose is less able to enter cells.

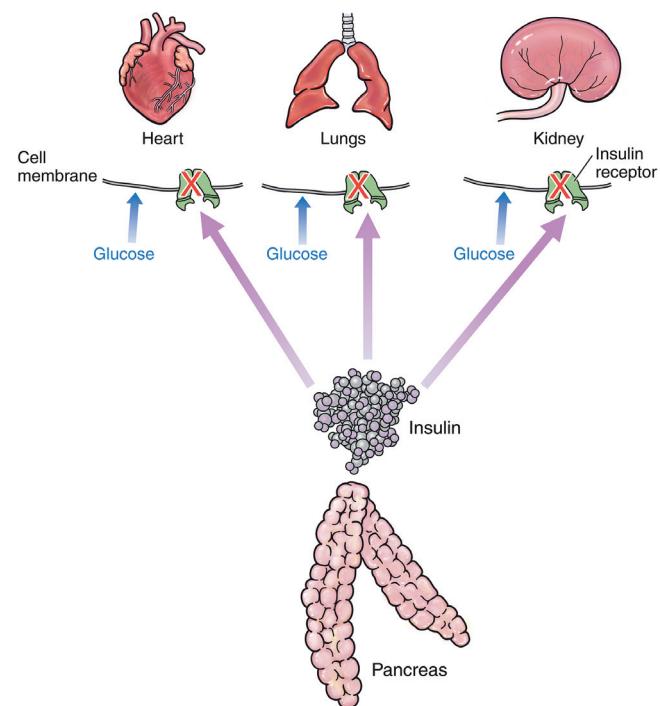


FIGURE 24-4 Type 2 diabetes mellitus is instigated by insulin resistance. The insulin receptor processes do not function appropriately, so fewer plasma membrane glucose transporters (GLUTs) are formed. Fewer GLUTs means that glucose is less able to enter cells. The body initially responds by producing more insulin. Chronic hyperfunction of the beta islet cells contributes to their eventual failure and the inability to secrete sufficient insulin.

immune-mediated destruction of beta islet cells but has also been described with exocrine pancreatic insufficiency.^{107,118,131} Type 2 DM is far more common in cats.⁹⁴ The initiating factor is insulin resistance (Figure 24-4). This may be associated with decreased number of insulin receptors,¹¹⁰ reduced receptor activity,¹¹⁵ direct effect on GLUT4,⁹ or a combination of factors. Initially, the body responds by producing more insulin. This chronic hyperfunction of the beta islet cells contributes to their eventual failure and the inability to secrete sufficient insulin.

Insufficient insulin production may affect potassium metabolism, insofar as insulin allows potassium to enter cells. In DM the lack of insulin or the lack of receptors means that less potassium is able to get into the cells. Hence there is an increase of potassium in the blood, which is cleared by the kidneys, especially with polyuria. Therefore serum/plasma potassium is even less reflective of the total body potassium than usual. In addition, insufficient insulin production may affect lipoprotein lipase (LPL) activity. LPL works in conjunction with insulin in fatty acid metabolism. The reduced LPL activity may be significant enough to result in lipemia. The lipemia may be due to triglycerides (TGs) or cholesterol, but TGs are more governed by chylomicrons (CMs) and very low-density lipoprotein (VLDL), which have more dependence on LPL activity.¹²⁷

Underlying Causes

Pancreatic Factors

Even without any overt exocrine pancreatic dysfunction, diabetic cats produce amylin (an amyloid precursor) that is deposited in islet cells, leading to decreased insulin production. In humans genetic assessments have indicated that many of the genes associated with type 2 diabetes are associated with insulin secretion from beta islet cells.¹⁰² Additionally, exocrine pancreatic disease occurs as a comorbidity with diabetes, and elevated serum feline pancreatic lipase immunoreactivity (fPLI) has been recognized in diabetic cats.³¹ Pancreatic diseases such as pancreatitis, pancreatic adenocarcinoma,⁹⁴ and genetic associations may play a role.⁶¹

Peripheral Factors

DM arises as a consequence of complex interactions of both pancreatic and multiple peripheral factors in any individual. The most common peripheral causes cited are age, gender, and breed predispositions as well as obesity, dietary carbohydrates, corticosteroid administration, and concurrent conditions such as infection.

Epidemiologic studies in cats consistently show DM to be a disease of older cats, with the incidence increasing markedly in cats over the age of 8 years.^{5,89,93,95} Age

associations with insulin resistance are controversial in people with discordant results, most likely because of general health, physical training, and changes in liver size.^{10,28} Multiple studies have indicated increased insulin resistance in male cats (in particular after neutering) that is consistent with the overrepresentation of males among diabetic cats.^{3,44,46}

There are now several studies indicating that Burmese are more at risk of DM than other cats in Australia, New Zealand, and the United Kingdom.* Breed predispositions are likely to be analogous to the situation for humans, wherein DM is more prevalent in various indigenous groups such as Australian Aborigines, African Americans, and Pima Indians.^{17,55,67} Genetic studies in humans have identified 20 common genetic variants associated with type 2 diabetes. Most of these genes are associated with regulation of insulin secretion from beta islet cells in response to insulin resistance, but there are also genes related to glucose transport and insulin sensitivity. Many associated genes have unknown roles. In most instances multiple genes are affected in individuals.¹⁰² The increasing availability of genome-wide assessments will make searches for specific genes easier in cats, but the complex interactions of multiple genes in humans may make interpretation more difficult in cats, wherein the number of cases assessed will be far less than in studies of people.

Obesity has been directly related to insulin resistance in cats as well as humans^{3,9} and specifically reduces GLUT4 expression.⁹ Other consequences of obesity in people, such as decreased insulin signaling and glucose disposal rates,⁶³ are also likely to be relevant in cats. For obesity (and insulin resistance generally) to be associated with type 2 diabetes, the beta islet cells must be unable to compensate fully for the decreased insulin sensitivity.⁶³ Weight loss is therefore an important component of diabetes management.

In comparison to most mammals, cats have very low hepatic activity of the enzyme glucokinase, which plays the important role of acting as a “glucose sensor.” Cats are able to compensate by having elevated levels of glucose 6-phosphate. This altered glucose-sensing pathway in the feline liver may represent an evolutionary adaptation to a low-carbohydrate diet.⁴³ These changes create challenges for all cats to handle the high glucose loads provided by high-carbohydrate diets and, if coupled with insulin resistance (from any cause), can result in diabetes. Recent studies have demonstrated improved remission rates when cats are fed low-carbohydrate/high-protein diets compared with high-fiber diets.^{7,32,76}

Specific infections in people (e.g., hepatitis C) have been correlated with insulin resistance,⁴⁷ although the reasons for the associations are not elucidated.

Additionally, tumor necrosis factor-alpha (TNF-alpha), a cytokine involved in systemic inflammation and the regulation of immune cells, has been demonstrated to play a role in the pathophysiology of insulin resistance.⁸ Managing underlying infections is an important component of reducing insulin resistance. Azotemia associated with renal disease¹⁸ and hyperthyroidism,⁵⁰ both common diseases in older cats, have also been demonstrated to contribute to insulin resistance. Management of concurrent conditions can therefore aid diabetic control.

Glucocorticoids impair insulin-dependent glucose uptake by peripheral cells and enhance hepatic gluconeogenesis as well as inhibiting insulin secretion from beta islet cells.² A recent study found that high doses of corticosteroids increased serum glucose in all 14 study cats assessed, but clinical signs were seen in only one cat.⁶⁸

Catecholamines and a number of other hormones released during stress states contribute to the development of hyperglycemia by directly stimulating glucose production and interfering with tissue disposal of glucose. In a normal individual hyperglycemia stimulates the secretion of insulin and inhibits the secretion of glucagon, effects that will diminish the degree of hyperglycemia resulting from direct actions of stress hormones on glucose production and disposal. Cats with impaired islet responses to glucose will be particularly prone to the development of marked hyperglycemia during stress states because they may be unable to respond to the influence of hyperglycemia.³⁹

Hyperglycemia itself suppresses the insulin response in three distinct ways that relate to chronicity of hyperglycemia:

1. Glucose desensitization: a normal physiologic response that is a rapid and reversible refractoriness of beta cells after short exposure to hyperglycemia
2. Beta cell exhaustion: a reversible depletion of the readily releasable pool of intracellular insulin caused by more prolonged hyperglycemia
3. Glucotoxicity: the slow and progressively irreversible direct toxicity of the beta cells induced by chronic hyperglycemia through functional change and cell death

A continuum exists between beta cell exhaustion and glucotoxicity in that the changes are reversible until a particular point in time.⁹²

Treatment Principles

It was not so long ago that the principle aims of therapy for diabetic cats were simply to control hyperglycemia safely (reduce the chance of ketosis) and resolve clinical signs of disease (e.g., polyuria, polydipsia, weight loss). Now the aim is to induce diabetic remission for as long as possible. Clinicians have better

*References 5, 62, 77, 95, 114, 121.

tools than ever (e.g., improved insulin and dietary therapy, home monitoring techniques) to achieve this more stringent goal. However, it must not be forgotten that successful treatment of DM includes an assessment of impact on quality of life for both cat and owner. Owners that perceive the treatment will have a negative impact on quality of life may be more likely to choose euthanasia over treatment.

Recently, a series of 29 specific DM-associated questions centered on both owner and animal were designed as a quality-of-life tool for diabetic cats. The tool was tested with 221 owners of diabetic cats predominantly in the United States and the United Kingdom, about half of whom performed home BG measurements. Nine of the top 10 items judged by owners to have negative impact were related to their own quality of life rather than that of the cat. These were issues such as difficulty boarding the cat, difficulty leaving the cat with family or friends, worry about the disease, worry about hypoglycemia, and changes to work and social life.⁸⁶

In a review of the pathophysiologic factors of type 2 DM detailed in the previous section, those factors that are unable to be influenced can be struck off, leaving those that should be addressed:

- Pancreatic factors
 - Reduced insulin
- Peripheral factors:
 - Age predispositions
 - Sex predispositions
 - Breed predispositions
 - Obesity
 - High-carbohydrate diet
 - Underlying infection
 - Corticosteroid usage
 - Concurrent conditions (e.g., azotemia, hyperthyroidism)

Therefore management of the diabetic cat should be a multipronged approach incorporating insulin, dietary therapy (to reduce carbohydrate load and induce weight loss if the cat is overweight), weaning off corticosteroids when possible, and management of any infection or concurrent condition. If peripheral insulin resistance factors can be overcome, the cat may be weaned from insulin *as long as the beta islet cells have not suffered irreversible damage from chronic glucotoxicity*. With early intervention and good glycemic control, diabetic remission was achieved in 84% to 100% of cats in two recent studies.^{73,104} Loss of control of peripheral factors such as a return to a high-carbohydrate diet, recurrence of obesity, or azotemia may result in a return to an insulin-dependent state.

Two recent studies have looked at factors associated with an increased chance of achieving remission. In one questionnaire-based study of owners of diabetic

cats treated with glargine insulin participating in an Internet forum, strict glycemic control, administration of corticosteroids before diagnosis, and absence of polyneuropathy were more likely in cats that achieved remission. Factors that were not useful predictors of remission included age, sex, body weight, and presence of chronic renal disease or hyperthyroidism. Cats that achieved remission had a lower mean maximum insulin dose (0.43 U/kg, every 12 hours) than cats that did not achieve remission (0.66 U/kg, every 12 hours).¹⁰⁴

In another study of 90 cats with newly diagnosed diabetes, 50% of cats achieved remission after a median time of 48 days. The maintenance insulin was glargine for 47% of cats and protamine zinc insulin (PZI) for 53% of cats. The median duration of remission was 151 days for cats still alive at the end of the study. Insulin was resumed in 29% of cats that had achieved remission, but six of the cats achieving remission did not require insulin again for more than 1000 days. In this study age and cholesterol levels were predictive of remission in multivariate analysis. Increased serum cholesterol decreased the chance of remission by about 65%. For each year of age, the chance of remission increased by approximately 25%. Duration of remission was longer with higher body weight and shorter with higher serum glucose. Cats treated with glargine insulin had an increased chance of remission based on univariate analysis.¹³⁵

Specifics of Treatment in the “Well” Cat with Diabetes Mellitus

Insulin therapy and dietary management are the mainstays for management of the basically “well” cat with DM that is not anorexic. The importance of weaning off corticosteroids when possible and management of any underlying infections or concurrent diseases should not be underestimated, but they are not specific to diabetic management.

Insulin Therapy

Insulin therapy provides the most effective and reliable means of achieving glycemic control in diabetic cats. The sooner glycemic control is reached, the higher the likelihood that diabetic remission can be achieved. A variety of insulin types can be used in cats for maintenance insulin therapy. It is difficult to predict in advance which cats will do better with which insulin, so the clinician must be knowledgeable about the insulin choices for treatment of feline diabetes. Although there are guidelines for choosing the starting dose of insulin for cats, the appropriate maintenance dose for each patient will be the dose that controls clinical signs and hyperglycemia. Most cats require twice-daily administration, regardless of the type of insulin selected. Because of the

TABLE 24-2 Characteristics of Insulins Commonly Used to Treat Feline Diabetes Mellitus

Insulin	Licensed in Cats	Manufacturer	Formulation	Action	Dose*
ProZinc	Yes	Boehringer Ingelheim Vetmedica	U40 recombinant PZI	Nadir 5-7 hours Duration 8-9 hours	Start 0.25-0.5U/kg, every 12 hours; Median maintenance dose 0.6 U/kg, every 12 hours
Vetsulin, Caninsulin	Yes	Intervet/Schering Plough	U40 Porcine zinc	Nadir 4 hours Duration 8-12 hours	Start 0.25-0.5 U/kg, every 12 hours; Median maintenance dose 0.5 U/kg, every 12 hours
Lantus	No	Sanofi Aventis	U100 Insulin glargine (recombinant human analog)	Nadir and duration not determined in diabetic cats	Start 0.25-0.50 U/kg, every 12 hours Median maintenance dose 2.5 U/cat, every 12 hours
Levemir	No	Novo Nordisk	U100 Insulin detemir (recombinant human analog)	Nadir and duration not determined in diabetic cats	Start 0.25-0.50 U/kg, every 12 hours Median maintenance dose 1.75 U/cat, every 12 hours

*Based on lean body weight.

unpredictability of the individual response to different insulins, it is important to be conservative when selecting insulin doses, either initially or when switching a cat from one type of insulin to another.

It is critical for veterinary staff and owners to be aware of the concentration of the insulin being used for a given patient and to use the correct syringes for the insulin to prevent dosing error. Most human insulins are 100 units/mL (U100), and micro-fine or ultra-fine U100 syringes should be used. Because cats often require very small doses of insulin, many owners find it helpful to use 3/10 cc (0.3 mL) syringes for U100 insulins. However, Caninsulin/Vetsulin and ProZinc are U40 insulin, and U40 syringes must be used. U40 insulins are often more suitable than U100 insulins for administration of the small doses that diabetic cats require.

The types of insulins most commonly used in cats can be summarized as follows ([Table 24-2](#)):

Long-acting insulins:

- Glargine (Lantus, Sanofi Aventis)
- Detemir (Levemir, Novo Nordisk)
- Protamine Zinc Insulin (ProZinc, Boehringer Ingelheim Vetmedica)

Intermediate-duration insulins:

- Porcine Lente (Vetsulin or Caninsulin, Intervet Schering Plough)
- Neutral Protamine Hagedorn (NPH; e.g., Humulin-N, Eli Lilly or Novolin-N, Novo Nordisk)

Rapidly acting, soluble insulin will be discussed below with therapy of diabetic ketoacidosis.

PZI-Vet (IDEXX Pharmaceuticals, Inc.), a 90% beef/10% pork U40 insulin, was commonly used in cats but is no longer commercially available because of the lack of a U.S. Food and Drug Administration-approved source of bovine pancreas. Compounded PZI cannot be recommended because the potency varies from batch to batch, making long-term regulation difficult. A replacement product based on recombinant human PZI insulin was developed and approved for cats as ProZinc (Boehringer Ingelheim Vetmedica) in 2009. One study that compared recombinant PZI (PZI-R, now sold as ProZinc) to PZI-Vet was conducted in six private feline specialty clinics. A total of 50 cats with DM and stable glycemic control on PZI-Vet (for at least 90 days) were switched to PZI-R for 30 days at the same dose rate and interval. In the 47 cats completing the study, there were no significant differences in body weight or serum fructosamine concentrations at days 15 or 30 compared with day 0. The researchers concluded that PZI-R provides glycemic control that is comparable to that of PZI-Vet when used at the same dose and dosing interval.⁸⁷

A prospective, uncontrolled 45-day clinical trial evaluating the efficacy of PZI-R (ProZinc) for controlling glycemia in cats with newly diagnosed, untreated diabetes (n = 120) and cats with previously treated, poorly controlled diabetes (n = 13) was also published recently. Treatment was started at 1 to 3 U/cat every 12 hours (0.22 to 0.66 U/kg every 12 hours), and the dose was adjusted at re-evaluations on the basis of the history and results of physical examination, body weight, and BG curves. Feeding the same diet to all cats was not attempted, although most cats were fed a high-protein/low-carbohydrate diet. The mean time of BG nadir was

between 5 and 7 hours, and subsequent BG concentrations were rising in most cats by 9 hours after administration. By day 45 the owner's subjective assessment of polyuria and polydipsia had improved in 79% of cats; 89% of cats had good body weight; and 9-hour mean BG concentration, serum fructosamine concentration, or both had improved in 84% of the cats compared with day 0. Biochemical hypoglycemia (BG less than 4.4 mmol/L [80 mg/dL]) occurred at least once in 64% of cats, and clinical signs of hypoglycemia were confirmed in two cats.⁸³

Vetsulin/Caninsulin, a porcine lente insulin, is a mixed insulin zinc suspension containing 30% amorphous zinc insulin (which is rapidly absorbed and has a short duration of activity) and 70% crystalline zinc insulin (which is absorbed more slowly and has a longer duration of activity). The onset and duration of action are shorter than that of PZI in cats, with a BG nadir at about 4 hours after injection, and a duration of about 8 to 12 hours.^{72,74}

A 12-month prospective study of Vetsulin/Caninsulin was conducted with 25 cats, most of which were newly diagnosed ($n = 15$), whereas the remainder were poorly controlled on other therapies. Cats with BG over 19 mmol/L (over 342 mg/dL) were started at 0.5 U/kg every 12 hours and cats with BG less than 19 mmol/L (less than 342 mg/dL) were started at 0.25 U/kg every 12 hours. No specific diet was fed. After an initial 6-day examination period, the cats were re-examined at 4, 8, 12, 26, and 52 weeks. Increases in insulin dose were made as needed, with a target BG nadir of 5 to 9 mmol/L (90 to 162 mg/dL). The median insulin dose was 0.5 U/kg every 12 hours (range 0.1 to 1.9 U/kg every 12 hours), and only two cats required doses higher than 1 U/kg every 12 hours. During the study period seven cats went into remission within 15 weeks, and none relapsed during the 12 months. Of the 18 cats that did not go into remission, 13 reached the water intake target established for ideal diabetic control (less than 20 mL/kg per day for canned diets, less than 70 mL/kg per day for dry diets). The control of clinical signs in the cats that did not achieve remission was deemed either excellent or good. It took approximately 3 months for significant resolution of clinical signs.⁷⁵

Another recent prospective, multicenter, nonblinded, open study followed 46 cats with diabetes (either newly diagnosed [$n = 39$], or previously treated but poorly controlled [$n = 7$]) during treatment with Vetsulin/Caninsulin. The cats were monitored for about 16 weeks (stabilization phase), with additional monitoring of some cats ($n = 23$) for a variable period. The starting dose for each cat was based on the initial BG concentration: 0.25 U/kg if the BG was less than 20 mmol/L (360 mg/dL), and 0.5 U/kg if greater than 20 mmol/L (360 mg/dL). The maximum starting dose did not exceed 2 U/dose, and dose rates greater than 0.5 U/kg twice daily were

not recommended during the first 3 weeks of treatment. No specific diet was used for all cats. At the end of the stabilization phase, 15% of cats achieved clinical remission. None of these cats had been treated previously for diabetes. Approximately 60% of the remaining cats were clinically stable after 3 to 4 months of treatment, a finding in line with studies published previously using a variety of insulins. Clinical signs of hypoglycemia were observed in nine cats during the stabilization period and were significantly associated with a dose of 3 U/cat or over 0.5 U/kg administered every 12 hours.⁷⁹

PZI and lente insulins, when administered twice daily, resulted in marked hyperglycemia (>18 mmol/L, 324 mg/dL) for several hours before each insulin injection in one study using nine healthy cats.⁷² The continued (though intermittent) hyperglycemia of such therapy most likely contributes to continued glucotoxic effects of permanently damaging beta islet cells and would explain why higher remission rates have been seen with glargine^{73,104} and detemir.¹⁰⁶

Glargine is a genetically engineered human insulin analog that has hormonal action identical to native insulin. When glargine is injected, it precipitates because of a pH change and forms microcrystals, which cause sustained release of the product. In humans glargine achieves long-lasting glycemic control and minimizes fluctuations in BG concentrations.

The recommended starting dose of glargine is 0.25 U/kg every 12 hours for cats with BG less than 20 mmol/L (less than 360 mg/dL), and 0.50 U/kg every 12 hours when the BG is over 20 mmol/L (over 360 mg/dL). One study in nine healthy cats showed that the nadir with glargine occurs approximately 12 to 16 hours after injection,⁷² whereas another study in five healthy cats using a euglycemic clamp showed the peak effect occurred between 2 and 9.75 hours.³³ Although it may appear that there is a discrepancy in reported time to peak action for glargine, it is likely a result of the very different study designs and different parameters each study used to define time to peak insulin action (nadir versus maximal glucose infusion rate). Put simply, the first study reported the time that nadir glucose occurred (based on actual BG concentration), whereas the second study reported the time of peak glucose infusion rate (to maintain normoglycemia). Further, these studies were performed with small numbers of healthy cats, and whether a similar response would be seen in diabetic cats is unknown. Individual cats with a glargine nadir after 12 hours may achieve adequate glycemic control with once-daily dosing, but twice-daily dosing is associated with better glycemic control and higher remission rates.^{73,124} Hence twice-daily dosing is recommended for most cats.

Detemir is an insulin analog that binds to albumin and is released slowly for a long duration of action. On the basis of studies by the manufacturer in humans, variations in BG with detemir may be even less

pronounced than with glargine. The duration of action and peak effect of detemir and glargine were evaluated in a study of five healthy cats. Definitive conclusions are hard to reach with small numbers of healthy cats, but the authors assessed that although glargine has a more rapid peak effect than detemir, it was more variable from cat to cat than detemir (glargine: 120 to 585 minutes; detemir: 370 to 575 minutes). The duration of action was longer for detemir in three cats but longer for glargine in two cats.³³

It is important not to mix or dilute detemir or glargine insulin because the duration of action depends on the pH of the product. Glargine (Lantus) is available in 10-mL vials and a 3-mL SoloSTAR pen that measures in 1-unit increments. However, the pen is expensive, cannot be refrigerated, and expires in 1 month. The cartridges for the pen can be dispensed to be used as individual 3-mL vials. If refrigerated, open vials of glargine or detemir can be used for approximately 6 months.⁹⁶ Detemir is available in 10-mL vials and a 3-mL FlexPen that measures in 1-unit increments. Once in use, the FlexPen is stored at room temperature and expires in 42 days. These insulins should be clear and colorless; if cloudiness, discoloration, or clumping is noted, the product should be discarded. It is not necessary to shake or rotate the vial before use. Glargin and detemir are not licensed for use in veterinary patients.

Two studies with the same protocols, except varying insulin type, found similar remission rates for glargine (84%)¹⁰⁴ and detemir (81%)¹⁰⁶ in diabetic cats starting therapy within 6 months of diagnosis. Remission rates were much lower if insulin therapy was started more than 6 months after diagnosis. The insulins were administered twice daily, and a low-carbohydrate diet was fed. Median time to remission was 1.7 months for cats receiving detemir and 1.9 months for cats receiving glargine. Most of the cats achieving remission were able to stay off insulin, and the median duration of remission was 10.8 months for glargine and 1 year for detemir. Although biochemical hypoglycemia was common, clinical hypoglycemia was rare, with only a single event with mild signs in one cat on each insulin. The median detemir dose was 1.75 U/cat every 12 hours, and the median glargine dose was 2.5 U/cat every 12 hours.

A direct comparison of insulin therapies in 24 newly diagnosed diabetic cats found remission rates were higher in those cats receiving glargine (100%) than PZI (38%) and lente insulin (25%) during the 16-week study period.⁷³ The initial dose of insulin was 0.5 U/kg ideal body weight if the BG on admission was greater than or equal to 360 mg/dL (20 mmol/L), and 0.25 U/kg if BG was less than 20 mmol/L (360 mg/dL). BG was measured every 2 hours for 12 hours for each cat for the first 3 days of treatment to ensure that cats did not become hypoglycemic. No increase in insulin dose was made during the first 3 days, even if persistent hyperglycemia

was present. During the study two cats treated with lente insulin and one cat treated with PZI had severe clinical hypoglycemia requiring intravenous glucose therapy. None of the glargine-treated cats exhibited signs of hypoglycemia, although many had biochemical hypoglycemia (BG less than 3 mmol/L [less than 54 mg/dL]) without clinical signs. By 16 weeks all eight cats in the glargine group had achieved remission, whereas two of eight cats in the porcine lente group and three of eight cats in the PZI group had achieved remission. The probability of remission in newly diagnosed patients fed a low-carbohydrate/high-protein diet was significantly greater for cats treated with glargine than cats treated with PZI or lente in this study.

One 12-week study of 13 diabetic cats found no significant difference in remission rates in cats receiving lente insulin (three of seven, 43%) compared to glargine (one of six, 17%). However, approximately half the cats enrolled in this study were not newly diagnosed with diabetes, cats received glargine only once daily but lente insulin twice daily, and monitoring was only every 4 weeks (after the initial 4 weeks).¹²⁴

The findings of these studies indicate that the greatest chance of achieving diabetic remission is prompt initiation of therapy with glargine or detemir insulin twice daily combined with dietary therapy and intensive monitoring to enable dose adjustments. However, remission has been achieved with all of the insulin types previously listed, and clinicians should become familiar with the usage of more than one type of insulin for feline patients. In countries where a legal obligation exists to use a product with a veterinary license first, PZI would be the first choice, if available, and porcine lente would be the second choice. Many factors must be considered when choosing insulin, such as product availability and affordability, convenience and ease of dosing, legal and licensing issues, and product support. In general, clinicians can expect good product support when using veterinary-licensed products in cats but no product support when using products licensed for use in human medicine.

INSULIN DOSING AND MONITORING PROTOCOLS

Managing diabetic cats with insulin with the objective of diabetic remission is a balancing act requiring sufficient insulin for glycemic control without causing hypoglycemia. The recommended starting dose for most insulins is 0.25 U/kg to 0.5 U/kg, with higher doses preferred for those cats with higher BG (more than 20 mmol/L [360mg/dL]) recognized at diagnosis.^{71,104,106} Frequent re-evaluations are required during the initial stabilization period, as outlined later and in **Box 24-1**. Typically, most cats first go through a phase where insulin dose is increasing, then stabilize when insulin dose is consistent, and then for cats achieving remission, a phase of decreasing insulin dose.

BOX 24-1**Suggested Treatment and Management Protocol for Cats with Nonketotic Diabetes Mellitus****At diagnosis**

- Evaluate for concurrent diseases with minimum database (complete blood count, serum biochemistry profile, urinalysis, urine culture, total T₄, feline pancreatic lipase immunoreactivity).
- Hospitalize for 1 day to begin insulin therapy; measure blood glucose every 3-4 hours, monitor for hypoglycemia.
- Consultation with owner to demonstrate insulin handling and injection techniques, discharge with written instructions on diet, monitoring for hypoglycemia, monitoring appetite and water intake, and so on. Introduce the concept of home blood glucose monitoring.

Three days later (this step not necessary for Lente insulin).

- Hospitalize for 1 day; measure blood glucose every 3-4 hours, and monitor for hypoglycemia.
- Consult with owner to confirm insulin handling and injection techniques.

One week later

- Re-evaluate body weight and condition, and perform full physical examination.
- Hospitalize to perform blood glucose curve, and adjust insulin dose as needed; preferably use the same portable blood glucose meter that the owners would eventually use at home, and validate by comparison to in-hospital chemistry analyzer.
- Consult with owner on home management of diet, and identify and correct any problems with insulin administration.

Repeat weekly in hospital blood glucose curves.

- Until owner feels confident to perform at home (can show owner each week)
- Or until appropriate nadir is achieved
- Confirm appropriate nadir 1 month later.

One month later

- Re-evaluate body weight and condition, and perform full physical examination.
- Hospitalize to perform blood glucose curve, and adjust insulin dose as needed.
- Consult with owner on any problems encountered with home care or monitoring.
- Discuss home blood glucose monitoring; demonstrate techniques, and provide supplies and written instructions.

Home monitoring

- Owner performs 12-hour blood glucose curve weekly until stabilized and telephones hospital to provide results.

Three months later and every 3 months subsequently

- Re-evaluate body weight and condition, and perform full physical examination.
- Evaluate home monitoring, including blood glucose measurements.
- Hospitalize for blood glucose curve.
- Compare hospital blood glucose curve and home blood glucose curve.
- Make insulin dose adjustments as required.
- Make adjustments to dietary therapy as required.
- Owner performs home blood glucose curve once monthly.
- Periodically repeat minimum database.

In human medicine, specialized educators provide most of the information on disease management, insulin injection and handling, BG monitoring, and so forth. In the veterinary setting this function is performed by the veterinarian or often by the veterinary nurse/technician. Owners must be properly trained to give insulin injections and educated on the important aspects of the disease in cats. For example, if some of the insulin dose is spilled during injection, the owner should be warned not to give additional insulin to avoid overdose. Whenever there is uncertainty about whether a dose has been administered, it is safest to wait until the next scheduled dose, because the consequences of missing one dose are negligible. Close contact with owners during the initial weeks of insulin therapy can help identify and correct any problems or misconceptions.

The owner and all members of the household should be aware of the clinical signs of hypoglycemia, which include lethargy, trembling, ataxia, altered mentation, seizures, and coma. If signs suspected to be caused by hypoglycemia are noted at home, the owner should be

instructed to give high glucose syrup orally. Suitable products are marketed for use by human diabetics. If the cat is unable to swallow, the syrup can be rubbed on the oral mucosa. When an episode of hypoglycemia occurs or is suspected, the owner should also seek veterinary care and discontinue insulin dosing in the meantime.

It is the authors' experience that hypoglycemia is rare initially, and if it is recognized biochemically within the first few days of therapy, there is a very low probability of clinical signs. Starting most diabetic cats at 0.5 U/kg increases the chance of establishing timely glycemic control. However, starting a cat on this dose of insulin requires close monitoring from day 1. When glargin was first introduced to management of feline diabetes, initial protocols called for BG testing every 4 hours for each of the first 3 days and then weekly.⁷¹ It is usually more practical to perform BG curves on day 1 and day 3. Long-acting insulins are marketed in human medicine as being peakless; this is not the case (at the very least in cats),⁷² and "spot" checks of BG are not adequate or appropriate to maintain glycemic control of diabetic cats. Serial BG

measurements (BG curves) are the most effective monitoring technique to establish what is happening with the cat's glucose homeostasis. Fructosamine assays are a crude measure reflecting the mean BG concentration for approximately the past week (compared with longer time periods in other species)⁶⁴ and are not an effective measure for tight management of glycemic control. High serum fructosamine concentrations indicate poor glycemic control but give no information about the nadir BG concentration and cannot be used to determine whether the insulin dose must be increased or decreased. In addition, some disease states, such as hyperthyroidism, affect fructosamine concentrations. Cats with overt, uncontrolled hyperthyroidism may have fructosamine concentrations below the normal range, probably as a result of metabolic changes.¹⁰¹

There is no uniformly recognized BG monitoring protocol for diabetic cats. High remission rates have been achieved with weekly in-hospital monitoring of BG curves (stretching to every 2 weeks after 4 weeks)⁷³ as well as with home monitoring up to daily and insulin dose changes instituted as often as every 3 days.^{104,106} The following schedule is suggested for BG monitoring either at home or in the hospital (serial measurements are taken on each day):

Long-acting insulins (see also Box 24-1):

- Day 1 (to monitor for early hypoglycemia)
- Day 3
- Day 10 (1 week later)
- Weekly until appropriate nadir (can be twice a week if monitored at home)
- Then confirm 1 week later
- 1 month later
- If monitored at home, once monthly
- In-hospital evaluation every 3 months for all cats (including those monitored at home)

BG can be evaluated every 3 to 4 hours. After an owner obtains a BG curve at home, especially during the stabilization period, the results should be reported to the clinician or veterinary nurse/technician. An appropriate BG curve for a stable diabetic cat being treated with long-acting insulin (e.g., glargine or detemir) is shown in Figure 24-5. A cat with a curve similar to the one illustrated needs no dose adjustment. However, cats can have such a curve yet need a dosage reduction (or increase) at a subsequent evaluation. In the early stages of treatment with long-acting insulins, the BG curve may resemble a curve obtained with lente insulin (Figure 24-6) with more distinct peaks but will usually flatten within 2 to 3 weeks. The slow absorption of glargine and detemir can result in atypical shaped curves with elevations of BG in the middle of the day (but this usually only occurs when there is minimal change in BG). Any dose adjustment decisions should be based on the lowest BG level of the day and should always take into account

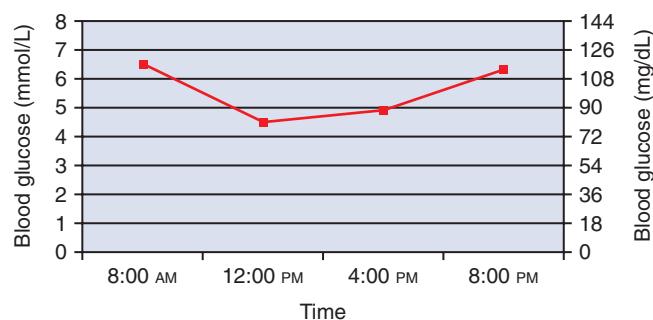


FIGURE 24-5 Ideal blood glucose curve for stable diabetic cat using long-acting insulin (e.g., glargine, detemir). Note that there typically is a nadir, but the variation from preinsulin blood glucose to nadir is not great.

the patient's clinical assessment (e.g., body weight, body condition score, appetite, water intake, and urine output).

Intermediate-acting insulins (e.g., lente) (see Box 24-1):

- Day 1 (to monitor for early hypoglycemia)
- Day 7
- Weekly until appropriate nadir (can be twice a week if monitored at home)
- Then confirm 1 week later
- 1 month later
- Every 3 months

An appropriate curve for a stable diabetic cat being treated with an intermediate-acting insulin (e.g., Vetsulin/Caninsulin or Humulin-N) is shown in Figure 24-6. Note the extended periods of time that BG remains above 15 mmol/L (above 260 mg/dL).

Common sense should be used when making any insulin dose adjustments. Suggested guidelines for dosage adjustments are shown in Table 24-3. Some guidelines for long-acting insulin dose adjustments also include recommendations based on the pre-insulin BG. The reason for monitoring is to assess the effect that particular dose of insulin has had, so changing the dose on the morning of testing defeats that purpose. The exception to this rule is when BG concentration is low before administration of insulin, in which case that dose should be skipped and the dose administered 12 hours later should be lower. As for long-acting insulins, dose adjustments should always take into account the patient's clinical assessment (e.g., body weight, body condition score, appetite, water intake, and urine output).

Once a cat achieves remission, ongoing BG monitoring should continue for the first month. Over the long term, urine glucose, body condition, appetite, and water intake can be monitored to detect loss of euglycemia. If hyperglycemia is detected, insulin therapy should be restarted promptly to avoid further damage to pancreatic beta cells. A low-carbohydrate, calorie-controlled diet often helps prevent obesity, minimize the demand on beta cells, and lower the risk of relapse.

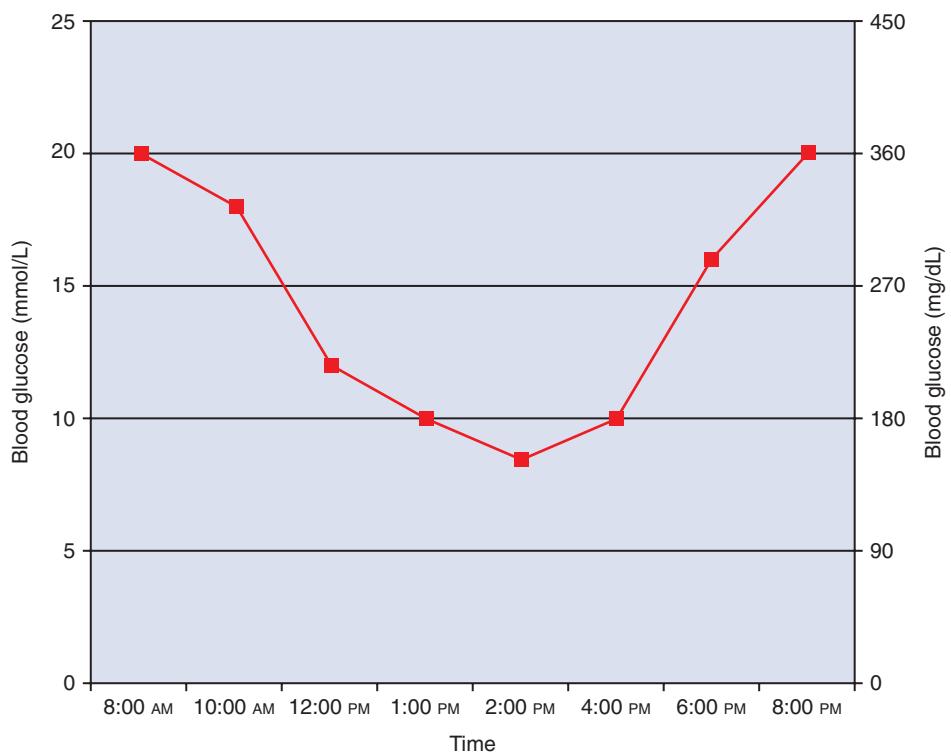


FIGURE 24-6 Ideal blood glucose curve for stable diabetic cat using intermediate-acting insulin (e.g., lente). Note the extended periods of time that blood glucose remains above the renal threshold.

TABLE 24-3 Suggested Guidelines for Insulin Dose Adjustment Based on Blood Glucose Curve Results

Insulin Type	Glucose Concentration	Insulin Dose Recommendation
Vetsulin	Nadir <3 mmol/L (54 mg/dL)	Reduce by 50%
Caninsulin	Nadir 3-4.5 mmol/L (54-81 mg/dL)	Reduce by 1 U
	Nadir 4.5-7 mmol/L (81-126 mg/dL)	Reduce by 0.5 U
	Nadir 7-10 mmol/L (126-180 mg/dL)	No change
	Nadir 10-12 mmol/L (180-216 mg/dL)	Increase by 0.5 U
	Nadir >13 mmol/L (234 mg/dL)	Increase by 1 U
	Pre-insulin <12 mmol/L (216 mg/dL)	Withhold and check for remission
Lantus	Nadir 4.5-9 mmol/L (81-162 mg/dL)	No change
Levemir	Nadir <4.5 mmol/L (81 mg/dL)	Reduce by 0.5 U
ProZinc	Clinical hypoglycemia	Reduce by 50%
	Pre-insulin <4.5 mmol/L (81 mg/dL)	Withhold and check for remission

Adapted from Rand J, Marshall R: Feline diabetes mellitus: which insulin do I choose & how do I adjust the dose? *Proc ACVIM Forum*, 2006; Nelson RW, Henley K, Cole C: Field safety and efficacy of protamine zinc recombinant human insulin for treatment of diabetes mellitus in cats, *J Vet Intern Med* 23:787, 2009; Marshall RD, Rand JS, Morton JM: Treatment of newly diagnosed diabetic cats with glargin insulin improves glycaemic control and results in higher probability of remission than protamine zinc and lente insulins, *J Feline Med Surg* 11:683, 2009.

CHANGING INSULINS

No washout period is needed to change insulin type. The new insulin can be substituted at the next scheduled dose. Recommendations for changing from one product to another for well-regulated cats include the following examples:

- From compounded PZI to ProZinc: Reduce the dose slightly, and perform a BG curve after 1 week and re-evaluate every 1 to 2 weeks until stable.
- From PZI-Vet to ProZinc: No dose adjustment is required; perform a BG curve 1 week later.

- From Vetsulin to ProZinc, Lantus, or Levemir or from PZI to Lantus or Levemir: It is not possible to extrapolate a dose, so the patient must be regulated on the new insulin as for a newly diagnosed patient; it is appropriate to start with 0.5 U/kg every 12 hours for most insulins.

In all cases, if a patient is currently not well regulated, the new insulin should be started at the recommended starting dose for the product and regulated as for a newly diagnosed patient.

GLUCOMETER CHOICE

Handheld glucometers to assess BG at the point of care have become standard in the management of DM in animals as well as humans. Only a limited number of glucometers have been critically assessed in the veterinary literature, with varying results.^{15,22,65,125,136} Accuracy is assessed by precision (variation of the individual glucometer for a particular sample) and bias (variation from a reference laboratory measurement). Accuracy is most often poor when very low or very high BG concentrations are measured.

Most glucometers are calibrated for human use. The distribution of glucose between plasma and red blood cells is different in feline blood compared with human blood. Glucometers for human use generally read lower (approximately 1 to 2 mmol/L [18 to 36 mg/dL]) than measurements from an automated chemistry analyzer. To further confuse matters, whole BG (measured with a glucometer) is approximately 10% lower than glycolysis-inhibited plasma glucose ("gray-top" tube samples); also compared with whole BG measurements, serum glucose reduces by approximately 5% to 7% per hour as a result of continued metabolism of glucose by the red blood cells.⁹⁷ Even glycolysis inhibitors contained in gray-top blood tubes (e.g., sodium fluoride/potassium oxalate) result in reduced plasma glucose readings when compared with promptly spun serum samples.¹²² Additionally, capillary BG measurements can be between 10% and 24% higher than venous whole BG in a nonfasted state.⁵⁸ Despite these multiple variations, studies in cats have shown minimal variation between samples obtained from the pinna versus peripheral vein,^{117,126} and a further study assessed glucometers by directly comparing capillary pinna samples to venipuncture collected samples.¹³⁶

The highest degree of accuracy among the glucometers tested to date has been shown with the AlphaTRAK glucometer (Abbott Laboratories), one of the few machines calibrated for use in veterinary patients. Although the AlphaTRAK is not as easy to use as human-medicine glucometers, it requires a very small sample volume (0.3 µL) and the test time is only 15 seconds. However, care must be taken with this glucometer insofar as it may be calibrated for canine or feline blood and accuracy is greatly diminished if it is set incorrectly.¹³⁶ The Ascencia Elite (Bayer Healthcare) glucometer has also been demonstrated to be accurate^{125,136} but reads lower than the AlphaTRAK and reference laboratory samples,¹³⁶ which potentially means that lower nadirs will be recognized.^{104,106} Other veterinary glucometers include GlucoPet and GlucoVet (Animal Diabetes Management, Janesville, Wisconsin), although they have not been critically assessed as of this writing. Glucometers should be selected carefully for use in practice and owners' use at home, with the clinician and owner

having an awareness of the bias of the glucometer compared with laboratory measurements of glucose. Ideally, the clinician would calibrate each glucometer used at home against the hospital's own blood chemistry analyzer or calibrated glucometer.

HOME MONITORING

Home monitoring is often used to refer to monitoring of BG values, but all owners also need to assess how well their cat is eating (either increased or decreased appetite) and drinking and whether its general behavior is normal. Ideally, all diabetic cats would receive daily monitoring at a minimum. The ability to record body weight at home is a very valuable monitoring tool. Owners should be encouraged to buy inexpensive scales suitable for measuring small patients (e.g., scales used to weigh human infants) and to keep a weekly log of body weight.

Most owners of diabetic cats are initially very concerned about their cat's diagnosis, and many are concerned about their ability to use syringes to inject insulin (although most soon find it is easier than giving oral medications to their cats), let alone take BG measurements. Home monitoring of BG is the goal, but clinicians should introduce these concepts to their clients and demonstrate how to obtain blood samples in a stepwise manner during visits in the stabilization period.

Perceived benefits of home BG curves include obtaining samples in a less stressful environment where the cat's food intake should be normal and the ability to perform more frequent BG monitoring. Many owners have the dedication and the ability to perform BG curves at home, but many do not realize this at first and can be intimidated by this prospect. As already noted, success is most likely when additional tasks for the owner of a newly diagnosed diabetic cat are sequentially introduced. Showing owners how to take a BG sample at the same time they are shown how to give an insulin injection for the first time is likely to reduce compliance. Some owners are happy to proceed with sampling their cat's BG after being shown only once; others need reassurance and multiple demonstrations. Common reasons for their initial reluctance to attempt home BG monitoring include fear of hurting the cat, fear of taking a blood sample, and concern over cost and time commitment. Watching an owner perform the procedure allows the clinician to identify and correct problems. Providing reliable and easy to understand educational resources as well as ready access to telephone support is also important.¹¹⁹ Long-term compliance with home BG monitoring is reportedly good, with 65% of owners performing it regularly in one study. Most owners in that study performed home BG curves every 2 to 4 weeks. Home monitoring provides owners with more confidence in their ability to manage their cat's disease.⁵⁴

Alternatively, some owners become overconfident in their interpretive abilities and will not seek continued

veterinary care until dramatic signs arise. It is important for owners to understand that information about protocols used to treat human diabetics cannot be applied to cats. In veterinary medicine, unlike human medicine, the goal in treating diabetes is not normoglycemia, because even some well-controlled diabetics can be at least slightly hyperglycemic at some time during the day.

In one study 12% of owners made changes to their cat's insulin dose without consulting the clinician. Owners should be cautioned against the temptation to make frequent changes to insulin dose and should make changes only after consultation with a veterinarian.⁵⁴ Another study found that approximately one fourth of cats had *higher* BG concentrations for 2 to 3 days after a glargine insulin dose increase.¹⁰⁴ The reasons for this are not known but may be associated with a lag time before feedback mechanisms adjust glucose homeostasis. The authors' experience is that the instinct of most owners is to further increase the insulin in this circumstance, sometimes on three consecutive days, which leads to an increased risk of hypoglycemia.

It must be emphasized that management of the diabetic cat is a team effort that includes the owner, the clinician, and often support staff such as veterinary technicians and nurses. Regular re-evaluations should be established to monitor weight and body condition score, look for underlying issues (e.g., dental infection), and confirm BG findings and discuss the owner's findings at home (see Box 24-1). One study has shown that the number of re-evaluations did not differ significantly between cats managed with and without home monitoring.⁵⁴ Once glycemic control has been achieved, diabetic cats should be re-evaluated approximately every 3 months.

BG concentrations measured at home have been compared with those measured in hospital in one study; surprisingly, hospital measurements were lower than those obtained at home.¹³ This may have been due to inappetence in hospital or stress from the less

experienced owner taking the sample at home. In about 40% of cats, the hypothetical treatment decisions based on the two methods of generating BG curves did not agree. Alternatively, it has been demonstrated that BG readings can be significantly higher in hospital (Figure 24-7).¹⁰⁰

Another study compared paired BG curves generated at home on 2 consecutive days in seven diabetic cats. In the second part of the study, two BG curves generated at home and one BG curve generated in hospital were compared. The results demonstrated considerable day-to-day variation in BG curves, even those obtained at home. The day-to-day variability between the home and hospital BG curves was not larger than between the paired home BG curves. There was less variability in the home BG curves obtained from cats with good glycemic control than from cats with moderate to poor glycemic control. These findings would indicate that a single BG curve may not always be reliable for making treatment decisions, whether performed in the hospital or at home.¹

In humans variations in BG concentrations occur within a 24-hour period as well as day to day and can be associated with activity level, meal size and type, stress, and some medications. Even when those factors are controlled, other factors, such as varying rates of insulin absorption from different injection sites and variation in length of insulin activity, cause day-to-day variability in BG concentrations. Many of these factors probably play a role in the variability of BG curves in cats as well. In particular, the role of absorption from different injection sites has not been investigated in cats. As more about day-to-day variability in BG measurements in cats becomes known, it is important not to rely solely on BG values but also to take into account the physical examination and other laboratory findings (e.g., weight loss or gain, urine specific gravity) and the owner's observations (e.g., appetite, water intake, activity level) when considering insulin dose adjustments.

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Please refer to the printed publication.

FIGURE 24-7 Blood glucose curve (BGC) at home and in the hospital 3 days later in a cat with diabetes mellitus (spayed female domestic shorthair, 4.7 kg). The cat was diabetic for 1 year and received 0.5 U/cat Caninsulin/Vetsulin every 12 hours at the time when the two curves were generated. According to the owner, the cat was doing well and had no signs of diabetes mellitus. The high blood glucose levels measured in the hospital were assumed to be stress-induced. Insulin dosage was not changed and the cat continued to do well. Blood glucose is noted in mmol/L; to convert to mg/dL, multiply by 18. (From Reusch C, Kley S, Casella M: Home monitoring of the diabetic cat, J Feline Med Surg 8:119, 2006.)

Sites that may be used for home BG sampling are the ear^{54,100,126} and the foot pads.¹³⁴ The pinnae (either the haired or nonhaired surface) are most commonly used to obtain samples (Figure 24-8). The ear should be warmed by rubbing or holding a heated cotton ball against the ear (the cotton ball can be heated by placing in a standard microwave for 10 seconds). The ear should not be cleaned or disinfected with alcohol. In longhaired cats, it may be helpful to shave a small portion of the pinna to improve visibility or to apply a thin film of petroleum jelly (petrolatum) to prevent the blood from dissipating into the fur. The opposite side of the ear can be stabilized with a cylindrical object, such as a roll of bandage tape. Then a lancet device or a 25-g hypodermic needle (without a syringe attached) can be used just near (but not directly over) the marginal ear vein to produce a blood drop. The test strip of the glucometer is then touched to the drop to absorb blood. While the machine is processing the sample, a piece of gauze or cotton ball can be used to apply pressure to the site to stop bleeding.

The main carpal (or tarsal) foot pads are usually easiest to use for sampling because they are the largest. Again, the pad should be warmed before a lancing device or hypodermic needle is used to prick the pad. Regardless of the site used for sampling, it can be helpful to place the cat in a favorite and comfortable spot for blood collection. The puncture site is usually not painful or visible.

Lancet devices are readily available from most pharmacists, and it is appropriate for the clinicians to have several brands in stock to try on individual cats because cats react differently. Two methods of capillary sampling from the ear have been described.¹²⁶ One method, using a conventional lancing device, was evaluated only in dogs but has also been used in cats. Alternatively, a lancing device that uses negative pressure (Ascensia Microlet Vaculance, Bayer Diagnostics) to help ensure a blood drop of adequate size can be used.⁹⁹

As may be expected, certain difficulties are commonly encountered when owners initially begin home BG monitoring, such as the need for assistance to restrain the cat, numerous attempts to produce a blood drop of sufficient size, and resistance from the cat. These difficulties tend to decrease over time as the owner gains experience with the technique.¹¹⁹

Continuous glucose monitoring systems have been designed to help human diabetics improve glycemic control and have recently been introduced in veterinary medicine. These devices measure interstitial glucose concentrations through a subcutaneously placed sensor. The sensor and transmitter are secured to the patient's back or side by bandaging. The data are relayed to a monitor that must be placed within several feet of the patient to record readings. Glucose readings are taken every 5 minutes, allowing for a large number of readings

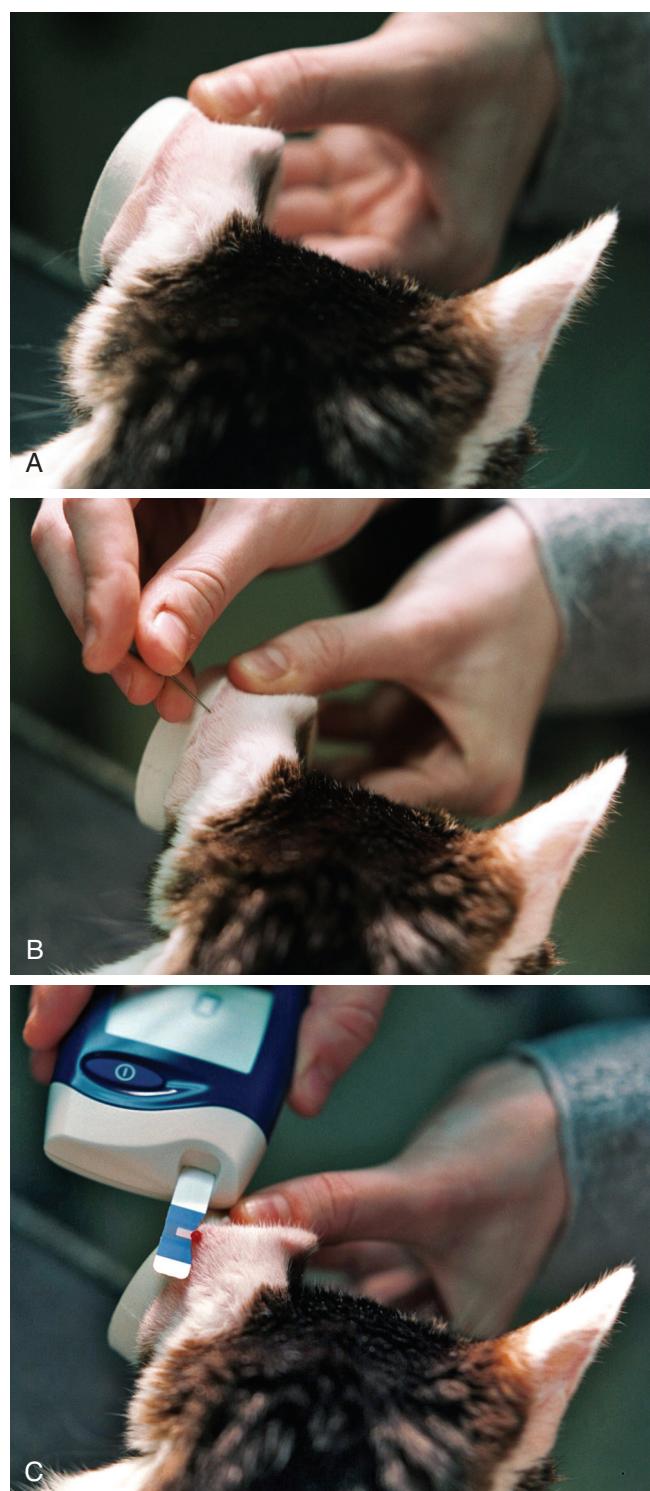


FIGURE 24-8 **A**, The pinnae are commonly used to obtain blood glucose samples. The opposite side of the ear can be stabilized with a cylindrical object, such as a roll of bandage tape. **B**, Then, a lancet device or a 25-g hypodermic needle (without a syringe attached) can be used just near (but not directly over) the marginal ear vein to produce a blood drop. **C**, The test strip of the glucometer is then touched to the drop and to absorb blood.

in a 24-hour period. Validation and use of these devices in cats have been described for both in-hospital and at-home use. Currently, drawbacks include the need for calibration every 12 hours and the need to remove the sensor after 72 hours, as well as the cost.*

Home monitoring urine for glucose and ketones may be an appropriate additional form of monitoring for some patients, particularly management of fractious cats. The main purpose of once- or twice-weekly urine monitoring is detection of uncontrolled hyperglycemia through persistently high urine glucose readings or, conversely, the detection of hypoglycemia through persistently negative urine glucose readings for cats receiving PZI or lente insulin. Persistently negative urine glucose readings may also indicate that diabetic remission is imminent. Negative urine glucose readings are commonly seen in well-controlled cats on glargine or detemir insulin. Owners should be cautioned never to change insulin dose solely on the basis of urine glucose readings.

Glucotest granules (Purina Veterinary Diagnostics) are a litter additive designed to detect glucosuria through a color change. In one study of the Glucotest granules, the glucose concentration was measured accurately in 29 of 48 feline urine samples. Of the inaccurate measurements, most were overestimates in the 2.8 to 16.6 mmol/L (50 to 300 mg/dL) range. Measurements taken at 8 hours were more accurate than immediate measurements. However, the researchers used frozen urine with added glucose rather than urine from diabetic cats, which may affect results.³⁰

Urine dipsticks are commonly used to measure glucose as well as other urine chemistries and may be used by owners at home. The accuracy of these sticks for feline urine is not well investigated. The ability of one brand (Bayer Multistix) to detect glucosuria in feline urine was determined by comparison to a chemistry analyzer. Sensitivity (73%), specificity (97%), and positive (73%) and negative (97%) predictive values were calculated. Overall, the accuracy of the test strip for classifying the urine glucose concentration in the correct interval was 91% (compared with 59% in dogs). Inaccuracies tended to be underestimates. The study was performed on urine samples submitted to a laboratory, however, whereas most owners are testing urine voided into a litter box, which may affect results.⁶ Well-regulated diabetic cats receiving PZI or lente insulin should have urine glucose readings between trace and 1+, although well-regulated cats on glargine or detemir insulin may have negative or trace readings. Persistent values outside this range should prompt the owner to seek veterinary advice.

Monitoring the fractious diabetic cat is a problem well known to most veterinarians. Fortunately, home

BG monitoring can often be performed for these patients, even if they require sedation to obtain BG samples in the hospital. Some difficult-to-handle cats can be restrained enough for safe access to the pinna or the saphenous vein or for placement of a heparinized catheter for repeat blood sampling. Results should be interpreted in light of stress, but it is the author's (RMB) experience that results consistent with clinical signs (and at-home results) can be achieved in most cases in these circumstances. Other tools owners can use for monitoring of these difficult patients include measuring water consumption, monitoring body weight and condition, and measuring urine glucose. Close attention should be paid to appetite, behavior, and so on. Periodic re-evaluation in the hospital, even if sedation is required, should include a full physical examination, serum fructosamine, and minimum database testing (complete blood count, serum chemistries, urinalysis, urine culture, total T₄) as required.

Oral Hypoglycemic Agents

Oral treatments for diabetes such as sulfonylurea agents (e.g., glipizide, glyburide) act by stimulating the pancreatic beta cells to produce insulin as well as potentiating insulin action.⁶⁰ These agents have been assessed in veterinary practice, with glycemic control reported in as many as 35% of diabetic cats.^{26,85} Unfortunately, there are no parameters that predict which cats will respond to sulfonylureas. The intrinsic problem with these agents is that the stimulation of any remaining functional beta islet cells to produce insulin can lead to beta cell exhaustion, which in turn leads to persistent hyperglycemia and possibly irreversible damage to beta cells. In addition, glipizide treatment may cause progressive amyloid deposition. Adverse effects include nausea, vomiting, anorexia, icterus, and elevated liver enzymes.⁴⁵

Oral hypoglycemics have no advantage over insulin therapy in terms of cost, time commitment, or frequency of re-evaluation. However, some owners that are initially unwilling to give insulin injections may be prevented from euthanizing their cat in a forced life-or-death decision when they are given the option of oral treatment. Some of these owners can eventually be persuaded to try insulin therapy. Within these parameters glipizide may be administered orally to nonketotic and otherwise healthy diabetic cats at a starting dose of 2.5 mg/cat, every 12 hours with a meal. If no adverse effects have occurred after 2 weeks of therapy, the oral dose may be increased to 5 mg/cat, every 12 hours.

Diet

Dietary management is an intrinsic part of therapy for diabetic cats (see Box 18-6). Three studies have specifically demonstrated better glycemic control and higher remission rates when canned low-carbohydrate diets

*References 19, 82, 98, 103, 128-130.

were fed.^{7,32,76} Other studies assessing insulin type and dosage have found high rates of remission when such diets are used.^{70,104,106} The optimal dietary level of carbohydrate for diabetic cats has not been defined, but all of these studies used diets with less than 12% carbohydrate as dry matter. By limiting dietary carbohydrate, BG is maintained primarily from hepatic gluconeogenesis, which releases glucose into the circulation at a slow and steady rate.⁵³

An earlier study showed that fiber-supplemented diets can improve glycemic control.⁸⁴ One study assessing both low-carbohydrate diets and fiber-supplemented diets found diabetic remission in cats eating each diet but notably higher remission rates for those eating low-carbohydrate diets.⁷ Remission in those cats eating the higher-fiber diets shows that carbohydrate load is only one aspect of glycemic control, as previously noted, with peripheral factors that contribute to diabetes.

More information about maintenance dietary requirements and weight loss strategies can be found in Chapter 18.

When It's Just Not Working! Insulin Resistance

As described in the previous sections, development of type 2 diabetes requires some degree of insulin resistance. The same term is used when the patient is resistant to exogenous insulin. There is no set dose that indicates insulin resistance; sometimes the required dose increases relatively quickly but then drops as glycemic control is gained. Suspicion of insulin resistance is raised when the insulin dose reaches 8 U/cat at each injection (just over 1.5 U/kg for a 5-kg/11-lb cat). This recommendation varies depending on the cat's weight; for example, a lean 7-kg cat receiving 8 U is receiving approximately 1 U/kg. The cat's body condition should also be taken into account, and U/kg should be based on the cat's normal weight. The BG nadir must also be taken into account, insofar as 1.5 U/kg may be an acceptable dose if the BG nadir is appropriate but may not be if there is minimal impact on BG levels. At approximately 1.5 U/kg at each injection in a poorly regulated cat, the clinician should start considering insulin resistance in earnest.

The following approach can be used for a cat when insulin resistance is suspected (Table 24-4). First, review the history, physical examination findings, and results from previous blood and urine testing. Were there uninvestigated clinical signs or biochemical abnormalities? Examples may include tachycardia and increased ALT (suggesting hyperthyroidism), hypercalcemia (suggesting malignancy, but having other causes as well), neutrophilia (suggesting underlying infection or inflammation), and hematuria (suggesting a urinary tract infection). Review of history and physical examination findings is important because mild changes may be

TABLE 24-4 Recognized Causes of Insulin Ineffectiveness or Insulin Resistance

Caused by Insulin Therapy	Caused by Concurrent Disorder
Inactive insulin	Diabetogenic drugs
Dilute insulin	Infection (oral and urinary especially)
Improper administration technique	Acromegaly
Inadequate dose	Hyperadrenocorticism
Somogyi phenomenon	Pancreatic pathology
Inadequate administration frequency	Hyperthyroidism
Impaired insulin absorption	Renal insufficiency
Anti-insulin antibody excess	Liver insufficiency
	Cardiac insufficiency
	Hyperlipidemia
	Pheochromocytoma

Adapted from Nelson RW: Insulin resistance in diabetic dogs and cats. In Bonagura JD, editor: *Kirk's current veterinary therapy XII*, Philadelphia, 1995, Saunders, p 390.

initially overlooked in the face of a persistent, significant hyperglycemia and glucosuria.

Ensure that the owner is administering insulin properly. Have the owner demonstrate insulin handling and injection technique using sterile saline, and correct any problems. Doses of U100 insulin less than 2 U can be difficult to measure reliably, and the minimum accurate dose for U40 insulin is 1 U. Owners with poor vision or arthritis may have difficulty measuring very small insulin doses. In households with more than one owner, ensure that all caregivers are administering insulin properly and consider the use of a chart that is filled out when a dose is given so that no insulin doses are missed. Ensure the insulin is kept in the refrigerator (if there is any doubt, start a new bottle) and that expired product is not in use.

Ensure that no nonprescribed medications are being given (consider medications from concurrent or previous veterinarians as well as nutritional or botanical supplements the owner may be administering). Re-examine the cat thoroughly. Look for obvious signs of infection, such as in the mouth, but also check nail beds, ears, and anal glands. Palpate the abdomen thoroughly, particularly for cranial abdominal masses (e.g., pancreatic adenocarcinoma), and note the size of organs (enlargement may suggest acromegaly). A urine sample (obtained by cystocentesis) should be submitted for culture and sensitivity testing, particularly if there is turbidity or hematuria. A serum biochemistry panel and total T₄ may be repeated depending on previous results and physical examination findings.

In the absence of any findings, start the cat on a course of broad-spectrum antibiotics (e.g., amoxicillin-clavulanic acid), start a new bottle of insulin, and continue weekly BG curves. If glycemic control is still not achieved, consider changing the type of insulin. Perform

thorough abdominal ultrasonography (looking for pancreatic pathology, liver changes other than fatty changes expected of diabetes, adrenal gland changes, or even generalized organomegaly that may be suggestive of acromegaly). Other tests that may be considered include a low-dose dexamethasone suppression test for hyperadrenocorticism and insulin-like growth factor 1 (IGF-1) assay or computed tomography (CT) for acromegaly. More information regarding hyperadrenocorticism and acromegaly are found elsewhere in this chapter.

Complications and Concurrent Conditions

Somogyi Effect

The *Somogyi effect* refers to rebound hyperglycemia that occurs as a counterregulatory response to hypoglycemia through the effects of adrenaline, cortisol, growth hormone (GH), and glucagon. It was first described by Dr. Michael Somogyi in 1938¹¹¹; this condition remains controversial in human medicine^{12,37} and is poorly described in cats.

A recent study has documented previously well-controlled diabetic cats with BG less than 2.2 mmol/L (40 mg/dL) followed by a fast, steep rise in BG concentration above 22 mmol/L (400 mg/dL) and/or concentrations that were at least 8 mmol/L (150 mg/dL) above the usually measured higher concentrations.¹⁰⁵ A similar scenario was recognized in cats that had not yet been well regulated but in which the preceding "hypoglycemia" was approximately 3.8 mmol/L (70 mg/dL). In both scenarios two subsequent insulin doses showed almost no effect, and the glucose concentration remained elevated for more than 24 hours. Four cats were recognized with one or other of these scenarios out of 55 cats assessed.

There are no specific guidelines for such a rare phenomenon, but if it is suspected, a prudent approach would be to withdraw insulin for 24 hours and then reintroduce it at a much lower dose, such as 50% of the previous dose.

Diabetic Neuropathy

Chronic hyperglycemia associated with uncontrolled diabetic mellitus results in neurologic structural abnormalities. Histologically, Schwann cell injury is most prevalent and includes myelin defects, such as splitting and ballooning and demyelination; axonal degeneration occurs in more severely affected cats.⁸¹ These changes are associated with microvascular pathology.²⁵ The most common clinical signs are a plantigrade posture when standing or walking, but a range of clinical signs is possible.⁸¹ The condition does not seem to be overtly painful, but most cats are irritable when their feet are touched or manipulated. The mainstay of treatment of diabetic neuropathy is achievement of glycemic control. Most animals have significant clinical improvement once consistent

euglycemia is achieved; however, persistent deficits are common.²⁰ Acetyl-l-carnitine has been shown to improve neurologic function in experimental animals and human patients,⁶⁹ but no clinical assessment has been made in cats.

Pancreatitis and Exocrine Pancreatic Insufficiency in Diabetic Cats

Given that the location of the insulin producing beta islet cells is within the exocrine pancreas, it is hardly surprising to expect exocrine pancreatic disease as a comorbidity. Direct associations of the endocrine and exocrine pancreas in cats have been recognized.^{29,31,34,109} Elevated serum fPLI in diabetic cats compared with nondiabetic cats was recently documented, but no association was made with degree of glycemic control.³¹ Another study found no association between glycemic control and pancreatic pathology.³⁴ Despite these findings, individual cats may have episodes of loss of glycemic control associated with pancreatitis, and the clinician should have a high index of suspicion if glycemic control is lost intermittently. There is no specific management to reduce this possibility in susceptible cats, and each episode must be managed on its own merits. The only overt clue of an episode of pancreatitis may be loss of glycemic control because clinical signs of pancreatitis in cats are nonspecific.¹²³

Exocrine pancreatic insufficiency (EPI) has been recognized concurrently with diabetes on few occasions.^{46a,90,112,116} This is hardly surprising because EPI is very uncommon in cats. A series of 16 cats with EPI found four nondiabetic cats with hyperglycemia (as well as a diabetic cat).¹¹⁶ BG should be assessed on a regular basis (e.g., every 3 months) in cats with recognized EPI. Pancreatic diseases are discussed further in Chapter 23.

Diabetic Crises

Diabetic crises result from relative or complete lack of insulin, an increase in counterregulatory hormones leading to gluconeogenesis and insulin resistance, a reduction in glucose utilization by peripheral tissues, hyperglycemia, and glycosuria with obligatory diuresis. The two most common diabetic crises are diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS), which is nonketotic.⁵⁶ Both conditions are initiated by a relative insulin lack, as with uncomplicated DM, but occur as a culmination of the cascade of events initiated by the body's response. Insulin retards lipolysis so that without insulin, adipocytes undergo lipolysis to release free fatty acids (FFAs) into the circulation. Circulating FFAs are taken up by the liver for TG production as well as for the manufacture of ketone bodies, which can become an additional energy source for most cells in the body. In uncomplicated diabetes TG production predominates and ketone production occurs

slowly enough that the ketones can be used by tissues for energy and will not cause hyperketonemia. In DKA relative increases of glucagon, epinephrine, cortisol, and GH occur compared with the decrease of appropriate insulin activity. An elevated glucagon:insulin ratio is characteristic of DKA. This change is usually caused by a stressful event; however, the inciting event may not be identifiable in every patient.⁵¹ In the far less common nonketotic HHS, it is believed that hepatic glucagon resistance and the presence of small amounts of insulin may inhibit lipolysis, thereby preventing ketosis.⁵⁶

Diabetic Ketoacidosis

Cats with DKA usually present for anorexia and lethargy. Cats are typically dehydrated on examination, and other signs are inconsistent. DM may not have been previously recognized. The key laboratory finding is ketosis, but cats are also acidotic and, of course, hyperglycemic.⁵¹ Ketones can be recognized in urine with urine dipsticks, and there are also plasma ketone dipsticks available. Plasma ketone dipsticks are unlikely to give a false-negative result, but the false-positive rate may be as high as 33%; conversely, urine ketone dipsticks are unlikely to give a false-negative result, but false-positive results may occur in 18% of cases. The tests can be used concurrently if there is any doubt about the result.¹³³ Some human glucometers (e.g., Optimum Xceed, Precision Xtra; Abbott Laboratories Ltd.) also have ketone test strips available. The latter monitor has been assessed in dogs, and although it tended to overestimate serum/whole blood beta-hydroxybutyrate levels, it still had good correlation with a reference laboratory analyzer and is recommended for use⁴¹; the use of such monitors in cats has not been critically evaluated.

In a recent study, 7 of 12 cats with DKA subsequently went into diabetic remission,¹⁰⁸ indicating that once DKA has been controlled, the overall prognosis for successful diabetic management is not necessarily worse.

Hyperglycemic Hyperosmolar Syndrome

The standard criteria for diagnosis of HHS (also known as *nonketotic hyperosmolar diabetes*) in veterinary medicine are documentation of a serum glucose concentration greater than 33 mmol/L (600 mg/dL), absence of urine ketones, and serum osmolality exceeding 330 mOsm/kg (or effective serum osmolality exceeding 320 mOsm/kg).⁵⁶ More information on calculating serum osmolality is found in Chapter 5.

Affected cats present similarly to those with DKA, with the exception that neurologic signs such as stupor and coma are more likely to be present. Azotemia is usually more severe. The only substantive study of HHS in cats (17 cases) found that cats with HHS were more likely to be older than DKA cats (mean age 12.6 years); more likely to be previously diagnosed as diabetic and

receiving insulin for several months (but not necessarily so); and more likely to have serious concurrent disease such as chronic renal disease, infection, congestive heart failure, neoplasia, and gastrointestinal tract disease. Prognosis was poor with 11 of 17 cats not surviving the emergency admission, and of these six survivors, only two lived longer than 1 year.⁵⁶

Management of Diabetic Ketoacidosis and Hyperglycemic, Hyperosmolar Syndrome

Management of DKA and HHS (Box 24-2) follow similar principles of correction of fluid and electrolyte imbalances and administration of soluble insulin such as Humulin-R (Eli Lilly), Novolin-R (Novo Nordisk), and Actrapid (Novo Nordisk). These insulins may also be referred to as "regular insulin" or "Toronto insulin," and although rapidly acting, they have a short duration of action. Parenteral fluid therapy, as well as correction of

BOX 24-2

Suggested Treatment and Management Protocol for Cats with Diabetic Ketoacidosis

1. Replace fluid and electrolyte deficits:
 - Fluid therapy: 0.9% saline for first hour, and then change to 0.45% saline (because most patients are hyperosmolar and there is potential for cerebral edema) or start with 0.45% saline
 - Administer fluids at 150 mL/kg every 24 hours, which is approximately 28 mL per hour for 4.5-kg (10-lb) cat.
 - Potassium: Add 30-40 mmol/L. (Note: This is approximately four times the maintenance amount for this rate of fluids.)
2. Insulin constant-rate infusion (use a separate bag of fluids, intravenous set, fluid pump):
 - Add 25 units of soluble/regular insulin to 500 mL fluids.
 - Run 50 mL of the insulin-containing fluid through the drip set.
 - Attach insulin infusion bag to Y-piece of fluid-replacement bag.
 - Administer insulin infusion at 1 mL/kg per hour.
3. Monitor:
 - Glucose and potassium every 4 hours until blood glucose is 10-12 mmol/L (180-216 mg/dL).
4. Maintenance, after blood glucose is 10-12 mmol/L (180-216 mg/dL):
 - Change the main fluid bag to 0.45% NaCl and 2.5% dextrose with 30 mmol/L KCl.
 - Reduce insulin infusion to 0.5 mL/kg per hour.
5. Discontinue infusion when the cat is eating, and manage as a stable diabetic.

Data from Church DB: Diabetes mellitus. In Kirk RW, editor: *Current veterinary therapy VIII*, Philadelphia, 1983, Saunders, p 838.

electrolyte abnormalities, for cats with DKA and HHS is covered in Chapter 5.

PARENTERAL FLUID THERAPY

DKA and HHS patients, by virtue of their poorly controlled diabetes, have relatively high fluid maintenance requirements. Consequently, providing intravenous fluids at approximately 150 mL/kg every 24 hours generally will provide some replacement and adequate maintenance; this works out to approximately 28 mL per hour for a 4.5-kg (10-lb) cat. The optimum fluid composition has not been determined for cats with DKA or HHS, and 0.9% saline has been advocated for initial use,^{35,52,56} with a change to 0.45% NaCl after the first hour. In most cases it is not only more convenient to start with 0.45% NaCl but may be more appropriate insofar as many DKA patients are also hyperosmolar (and HHS cats are by definition). The addition of 30 to 40 mmol/L of potassium chloride (KCl) reduces the hypotonicity of the solution. Note that this is approximately four times the maintenance amount of potassium for this rate of fluid administration; this is important because the lack of relative insulin means that potassium is being restricted from entering cells, as well as glucose. Plasma measurements are always of extracellular potassium, and in a diabetic cat this provides an even further underestimation of total body potassium than is normally the case. Whereas one aim is to rehydrate the patient, the other must be to provide some measure of diabetic control, or at least inhibit ongoing peripheral lipolysis and hence start to reduce the potential for ketoacidosis.

INTRAVENOUS INSULIN THERAPY

For treatment of clinically significant ketoacidosis, insulin may be administered by constant-rate infusion (CRI) or by intramuscular injection. In both situations the insulin should be in a soluble and hence relatively rapidly acting form. Although an intravenous insulin infusion may sound daunting, it is certainly the simplest and least labor-intensive means of treating diabetic patients who are inappetent.

One method for administering insulin by CRI is to add 25 units of soluble insulin to 500 mL fluids, producing an insulin concentration of 50 µU/mL. Insulin adheres to glass and plastic surfaces, so approximately 50 mL of the insulin-containing fluid should be run through the drip set before it is attached to the patient. This ensures that the animal receives a constant insulin concentration in the administered fluid.⁹¹ Because the standard insulin infusion rate to inhibit gluconeogenesis, but not unduly enhance extrahepatic glucose utilization, is 40 to 60 µU/kg per hour,¹⁴ the CRI can be administered at 1 mL/kg per hour of this solution. Obviously, a flow rate of approximately 1 mL/kg per hour is inadequate for maintenance fluid requirements. Consequently, the insulin CRI must be administered through

a second infusion line (Figure 24-9), usually attached to the Y-piece of the maintenance fluid line.

The insulin is infused at a rate of 1 mL/kg per hour until plasma glucose concentrations fall to 10 to 12 mmol/L (180 to 216 mg/dL). At this time the flow rate should be halved (0.5 mL/kg per hour), and a concurrent dextrose infusion introduced through the maintenance fluid line. One simple and effective means of achieving a balance between the insulin and glucose infused is to change the maintenance fluids from 0.45% sodium chloride (NaCl) and 30 mmol/L KCl to 0.45% NaCl and 2.5% dextrose with 30 mmol/L KCl and administering this combination at 150 mL/kg every 24 hours. This will produce a glucose infusion rate of approximately 150 mg/kg per hour, which should balance the insulin being infused at 0.5 mL/kg per hour.

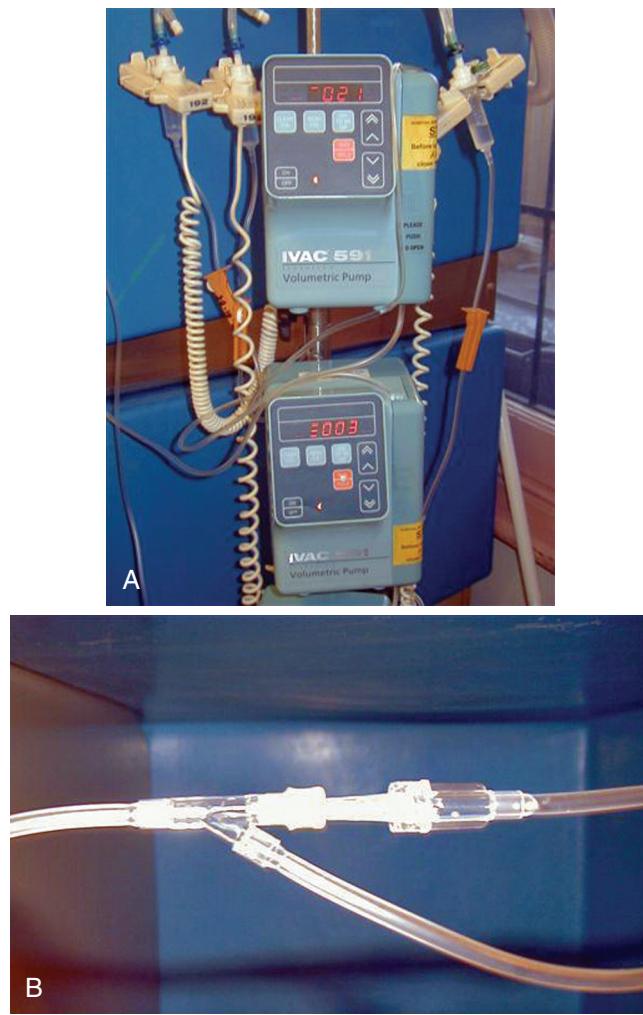


FIGURE 24-9 A, Two fluid pumps used to treat a cat with diabetic ketoacidosis. The cat weighs 3 kg, and the pump set at 21 mL per hour is delivering 0.45% NaCl with 40 mmol/L of potassium added. The pump set at 3 mL per hour has 25 units of soluble insulin added to a 500-mL bag of fluids. B, This second pump runs to a Y-piece so that only one intravenous catheter is needed.

During this time the patient's BG and serum potassium (and other electrolytes) are checked regularly. Over a period of 48 to 72 hours, the BG should remain relatively steady, ketonemia should disappear in DKA cats, and generally these patients should return to normal water and nutrient intake. Prognosis is more guarded in HHS cats, and management of concurrent conditions can affect how smoothly this protocol can be followed. For example, congestive heart failure is a contraindication to administering high fluid rates. Once initial abnormalities resolve, it is likely that, at least in the short term, the patient will be stabilized on a regular feeding regimen and an insulin dose regime appropriate for a stable diabetic cat, as outlined earlier in the chapter.

Other adjustments (e.g., of magnesium and bicarbonate) should be made only on the basis of measurement of these parameters. Acidosis usually resolves without addition of bicarbonate. Magnesium can be infused at 1 mEq/kg every 24 hours if hypomagnesemia is recognized.⁴² Magnesium toxicity has been reported when administered unnecessarily.⁴⁸

INTRAMUSCULAR INSULIN

Intramuscular (IM) protocols have been described and can be used as alternatives to the CRI insulin protocol outline in the preceding section; however, they are far more labor intensive. Two protocols have been described: hourly IM insulin²⁷ and intermittent IM insulin.¹¹

For the *hourly IM insulin* protocol, soluble insulin should be administered at an initial IM dose of 0.2 U/kg, then 0.1 U/kg hourly thereafter. BG should be monitored hourly. When BG concentration falls below 16.5 mmol/L (approximately 300 mg/dL), 5% dextrose solution should be added to the intravenous fluids and insulin dosing frequency should be reduced to 4- to 6-hour intervals, administered intramuscularly.²⁷

For the *intermittent IM insulin* protocol, 0.25 U/kg soluble insulin should be administered intramuscularly as a test dose, with subsequent doses based on the patient's response to initial treatment. In obese cats the initial dose should be based on estimated lean body weight to avoid overdosage and hypoglycemia. BG should be rechecked at 4- to 6-hour intervals; the goal is to reduce BG by 3 to 4 mmol/L per hour (54 to 72 mg/dL per hour). If this goal is surpassed, the next insulin dose should be reduced by 25% to 50%. If this goal is not met, the next dose should be increased by 25% to 50%. If the BG level reaches 10 to 12 mmol/L (180 to 216 mg/dL), 2.5% to 5% dextrose should be added to the intravenous fluids.¹¹

As with the CRI insulin protocol, once BG returns to normal and the ketonemia resolves, the cat should be started on a dietary and insulin therapy appropriate for a stable diabetic.

GASTRINOMA

Functional pancreatic islet tumors that secrete gastrin have been infrequently described in cats.* Gastrin secretion results in the release of hydrochloric acid by the gastric parietal cells, and increased gastrin production typically results in gastroduodenal ulceration and potentially perforation. Reported cases were 8 to 12 years of age, with no sex or breed predispositions recognized in such a small sample. All cases presented with vomiting, weight loss, and poor body condition. Clinical and ancillary test results were not consistent, but possible findings include anemia (mild or severe and regenerative or nonregenerative, depending on the degree and rate of blood loss), a palpable abdominal mass, and an ultrasonographically visible pancreatic mass. One or several pancreatic masses were recognized at surgery or necropsy in all cases. Resected masses immunostain positive for gastrin. Fasting serum gastrin levels were elevated (as expected) in all cases evaluated. Surgical resection of pancreatic masses may be curative, but lifetime ancillary treatment with H₂-receptor antagonists such as cimetidine or ranitidine or, perhaps better, proton pump inhibitors such as omeprazole is warranted. Two cats were alive when their cases were described at 12 months²³ and 17 months, respectively,²¹ after surgery. Another case survived 18 months until omeprazole was discontinued.⁶⁶

INSULINOMA

Insulinoma is an islet cell carcinoma that secretes insulin, and very few cases have been described in cats.[†] Elevated insulin results in hypoglycemia, and resultant clinical signs include seizures, weakness, and localized muscle twitching. Documented cases have been 12 to 17 years of age, and three of the six described cases have been Siamese cats. Diagnosis is suspected by recognition of hypoglycemia with concurrent hyperinsulinemia and confirmed by finding pancreatic islet carcinoma on histologic examination of biopsy samples. The tumor should stain positive for insulin by immunocytochemistry. Only one published case has had prolonged survival beyond surgical resection, being 32 months after surgery when reported.³⁶ Recurrence of clinical signs occurred at 5 days, 6 days, 1 month, 7 months, and 18 months postoperatively in other cases.^{40,57,78,88} In one of these cats, metastases to the pancreatic lymph nodes and liver were found at postmortem examination.⁴⁰ Frequent feeding and oral prednisolone allowed successful management

*References 21, 23, 66, 80, 88, 113, 120.

†References 36, 40, 49, 57, 78, 88.

for an additional 8 and 24 months in two cats^{40,88} but was unsuccessful in another.⁷⁸ Cellular and molecular characterization in a recent case determined that the tumor secreted several peptide hormones in addition to insulin—namely, chromogranin A and somatostatin—but not glucagon or pancreatic polypeptide. It was also recognized that the tumor expressed several genes characteristic of pancreatic beta cells, including insulin (*INS*), glucose transporter 2 (*GLUT2*), and glucokinase (*GCK*). The tumor also expressed hexokinase 1 (*HK1*), a glycolytic enzyme not normally expressed in beta cells. *GCK* expression was higher in the insulinoma than in normal pancreas from the same cat. The *GCK*: *HK1* ratio was twentyfold higher in insulinoma tissue than in normal pancreas. These findings suggest insulinoma cells may have an increased sensitivity to glucose that could contribute to the abnormal insulin secretory response observed at low serum glucose concentrations.⁴⁹

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THYROID GLAND DISORDERS

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HYPERTHYROIDISM

Hyperthyroidism refers to an increase in the functional thyroid hormones, thyroxine (T_4) and tri-iodothyronine (T_3), most commonly due to benign thyroid adenoma or adenomatous hyperplasia present in one or both lobes of the thyroid gland. Resultant clinical signs are variable but typically include weight loss, often with increased appetite, hyperactivity and cardiovascular signs; at least one lobe of the thyroid gland is palpable in most cases.

Epidemiology

Hyperthyroidism is commonly cited as the most common endocrinopathy of cats^{28,63,89,130} and most clinicians' anecdotal experience would bear this out. However, different studies have used different measures of disease rates, and there are also likely to be geographical variations in disease occurrence rates. In one study, reported in 2005, an annualized incidence rate of 11.92% was recognized in cats older than 9 years of age at a primary accession practice in London compared with 1.53% in Spanish practices.¹⁴³ The hospital prevalence among cats older than 8 years of age in an urban population of cats in Germany was noted as 11.4% in 2006.¹¹² In Japan, in 2002, a prevalence of 8.9% was noted in cats older than 9 years,⁷⁰ and in Hong Kong, in 2009, a prevalence of 3.93% was recorded in cats older than 10 years.²⁴

Despite these high disease rates, hyperthyroidism is a new disease that was first described in 1979.⁹³ Before this time enlargement of the thyroid gland had been

found at necropsy in cats and nodules were observed histopathologically, but these abnormalities were relatively rare and were not associated with the clinical signs relating to hyperthyroidism.^{61,62} Since this first description, several studies have documented marked increases worldwide with time—for example, from 0.3% in 1979 to 4.5% in 1985 in North America¹¹³; from 0.1% in 1978 to 1982 to 2% in 1993 to 1997, also in North America²⁷; and from 0.2% in 1987 to 1994 to 2.6% in 1998 in Germany.⁵⁹

The sudden appearance and subsequent increase in rates of this condition have led to investigations of potential underlying causes. These studies have indicated that numerous environmental and nutritional factors play a role in the pathology of this disorder.

A number of studies have pointed to consumption of canned food as a risk factor,* which is ironic because dry food consumption is considered a risk factor for DM, the next most common endocrinopathy in cats. "Pop-top" cans may pose more of a risk than cans for which a can opener is required^{27,142} or packets.¹⁴² This is potentially because of the release of chemicals such as bisphenol-A and bisphenol-F from the lacquer linings of the cans during the heating process. Higher amounts of these two chemicals have been found in high-fat foods from pop-top cans than in high-fat foods from other types of cans. The two studies that found pop-top cans to increase risk also found fish consumption (canned or home cooked) to provide increased risk of hyperthyroidism.^{27,142} This is compared with other studies that did not find an association with fish consumption.^{27,53,79,113} Soy protein in the diet has been demonstrated to increase thyroxine concentrations in cats,¹⁴⁸ and soy isoflavones were identified in nearly 60% of cat foods tested (dry, moist, and semimoist).²⁰ One study found that cats that consumed commercial foods without iodine supplementation were more than four times as likely to develop hyperthyroidism as cats that ate iodine-supplemented foods.^{26a}

Environmental factors that have been associated with increased risk of developing hyperthyroidism include use of insecticidal products such as antiflea products^{53,79,113} for the cat or fly sprays^{79,113} within the household; exposure to herbicides, fertilizers (e.g., from water from puddles in households where these are used)^{79,113}; and flame retardants that were introduced into routine use for building materials, electronics, furnishings, foams, and textiles at approximately the time hyperthyroidism was first recognized.²⁶

Pathogenesis

The increases in T_4 and T_3 that cause clinical hyperthyroidism result from normal thyrocytes becoming

*References 27, 53, 65, 79, 113, 142.

hyperfunctional because of adenomatous hyperplasia or adenoma.⁸⁴ Thyroid carcinoma is relatively rare, occurring in up to only approximately 4% of cases,^{47,74} and it has been suggested that such malignant thyroid tumors could have a different pathogenesis¹⁰² than the typical benign lesions.

The feline thyroid gland normally contains a subpopulation of the follicular cells that have a high, intrinsic growth potential. In the thyroid gland eventually destined to develop adenomatous hyperplasia, this subpopulation of thyrocytes may replicate in an autonomous fashion. Once these rapidly dividing cells are present in sufficient numbers, they may continue to grow in the absence of extrathyroidal stimulation, such as thyroid-stimulating hormone (TSH). Therefore these thyroid adenomatous hyperplastic cells show autonomy of growth, as well as the ability to function and secrete thyroid hormone in an autonomous fashion.⁸⁴ Large case series have consistently demonstrated that bilateral thyroid involvement is present in more than 70% of hyperthyroid cats. This may be important in pathogenesis insofar as no physical connection exists between the two thyroid lobes in cats.^{6,98}

In normal thyroid cells, after the TSH binds to its receptor, G proteins are activated that control the initiation of adenylate cyclase activation and cyclic adenosine monophosphate (cAMP) levels. G proteins couple to the TSH receptor and can be stimulatory (Gs), resulting in an increase in cAMP, or inhibitory (Gi), resulting in a decrease in cAMP. The relative amounts of Gs and Gi proteins determine the ultimate levels of cAMP in the cell. If the balance is altered in favor of Gs, by overexpression of Gs or underexpression of Gi, it results in overproduction of cAMP and overactivation of the thyroid cell. One study looked at eight hyperthyroid cats and four age-matched euthyroid cats and examined them for Gs and Gi protein expression. Gs expression was identical in both hyperthyroid and euthyroid cats, but Gi expression was significantly decreased in the hyperthyroid cats, suggesting that G protein expression regulating cellular cAMP levels may play a role in the pathogenesis of feline hyperthyroidism.⁴¹

Clinical Signs

Hyperthyroidism most commonly occurs in middle-aged to older cats. Most large series of cases have found a mean or median age of 12 or 13 years, with only 5% of cases diagnosed in cats younger than 10 years of age. There is no definitive breed or sex susceptibility, but some papers have shown a skew to increased numbers of females.^{69,100}

The typical historical findings and clinical signs of hyperthyroidism, together with indicative frequencies, are shown in Table 24-5. These frequencies are noted from a 1995 paper that assessed changes in clinical and

TABLE 24-5 Clinical Findings in Cats with Hyperthyroidism¹³

Finding	Percentage of Cats
HISTORICAL OWNER COMPLAINTS	
Weight loss	88
Polyphagia	49
Vomiting	44
Polyuria/polydipsia	36
Increased activity	31
Decreased appetite	16
Diarrhea	15
Decreased activity	12
Weakness	12
Dyspnea	10
Panting	9
Large fecal volume	8
Anorexia	7
PHYSICAL EXAMINATION FINDINGS	
Large thyroid gland	83
Thin	65
Heart murmur	54
Tachycardia	42
Gallop rhythm	15
Hyperkinesis	15
Aggressiveness	10
Unkempt hair coat	9
Increased nail growth	6
Alopecia	3
Congestive heart failure	2
Ventral neck flexion	1

laboratory findings in cats with hyperthyroidism from 1983 to 1993, finding lower frequency and severity of signs in the latter year¹³; similarly, the severity of cardiac changes reduced over a similar duration, though the percentage of cats with a murmur remained similar.³⁴ This reduction in frequency and severity of signs most likely arose from veterinarians' awareness of this new condition, and there may well have been further changes in clinical awareness, and therefore clinical signs that are seen, since 1993. Though reduced in frequency and severity, the general signs recognized remain the same.

Thyroid hormones regulate metabolic processes, so increased circulating levels of these hormones result in the increased appetite, weight loss, and muscle wastage that are typical of hyperthyroidism in cats. Thyroid

hormones also appear to interact with the central nervous system, increasing sympathetic drive and resulting in the hyperexcitability, nervousness, tachycardia, and perhaps tremor that are also characteristic for hyperthyroidism.¹⁰¹

Weight Loss

Hyperthyroidism should be considered in all middle-aged to older cats that have lost weight. The differential diagnoses for weight loss are extensive, including primary gastrointestinal disease, neoplasia of any origin, and renal disease. Hyperthyroidism, however, is so common that it should always be considered, whether or not supporting signs such as tachycardia are present. Further, weight loss is the most commonly recognized sign of hyperthyroidism.¹³ Weight loss is often associated with increased appetite, but some cats have the same, or even reduced, appetite.

Heart Murmur and Other Cardiac Signs

Cardiac signs of some description are present in approximately 50% of cats with hyperthyroidism.^{34,69} Therefore, as for weight loss, hyperthyroidism should be considered in any older cat with cardiac signs. The most commonly auscultated change is a murmur or tachycardia; also, the intensity of each heartbeat is often more pronounced and feels almost like a pounding on the clinician's eardrums. Typical echocardiographic abnormalities include hypertrophy of the left ventricular free wall (approximately 70% of cats), left atrial and ventricular dilation (70% and 45% of cats, respectively), and hypertrophy of the interventricular septum (40% of cases). Myocardial hypercontractility, manifested by increased fractional shortening and velocity of circumferential fiber shortening, is often found.⁹ These changes can (uncommonly) result in congestive heart failure and even aortic thromboembolism.

Mild to moderate hypertension, reversible upon induction of euthyroidism, was originally considered important in hyperthyroid cats.^{58,118} However, it is now clear that hyperthyroid cats are typically only mildly hypertensive, if at all, and when present may simply reflect the reduced tolerance of hyperthyroid cats to stressful situations such as veterinary examinations ("white-coat phenomenon").¹¹⁷ In accordance with this, hypertension-associated blindness and obvious ocular abnormalities are uncommon in hyperthyroid cats even in the presence of documented hypertension.¹³² Although hyperthyroidism is associated with increased cardiac output, there is a decrease in systemic vascular resistance mitigating against the development of significant hypertension.¹¹⁹ If moderate to severe hypertension and its effects are demonstrated in a hyperthyroid cat, other potential causes such as chronic renal disease should be considered. Interestingly, some cats appear to develop hypertension after successful treatment of hyperthyroidism, and this may result, at least in part, from the increase

in systemic vascular resistance as thyroid hormone concentrations decrease or from the associated decline in renal function.^{119,120}

Cardiac and blood pressure changes, like most other signs of hyperthyroidism, are mostly reversible on treatment of the underlying endocrinopathy.¹⁰¹ In some cases, however, cardiac changes may persist or worsen after treatment, suggesting a preexisting cardiac defect or thyroid hormone-induced irreversible structural damage.⁹

Palpable Thyroid Gland(s)

At least 80% of hyperthyroid cats have at least one palpable thyroid lobe.¹³ The normal thyroid lobes are not palpable because they are flat (2 to 3 mm thick) and lie ventrolateral to the trachea and dorsal to the medial borders of the sternothyroideus and sternohyoideus muscles.²⁸ There are several techniques to palpate thyroids:

- **Classic technique:** The cat is restrained in sitting position and the front legs held still. The neck of the cat is extended, and the clinicians' thumb and index finger are placed on each side of the trachea and swept downward from the larynx to the sternal manubrium (Figure 24-10). Palpation of a mobile subcutaneous nodule or a "blip" that slips under the fingertips determines the presence of a goiter.¹⁰¹



FIGURE 24-10 Classic thyroid palpation technique: The neck of the cat is extended, and the clinician's thumb and index finger are placed on each side of the trachea and swept downward from the larynx to the sternal manubrium. The thyroid is circled.



FIGURE 24-11 Norsworthy thyroid palpation technique: The cat's head is turned (45 degrees) from the side being assessed. The clinician's index finger is placed in the groove formed by the trachea and sternothyroid muscle just below the larynx and then moved downward in the groove to the thoracic inlet. The position of the thyroid lobe is circled. The technique is more successful when just the index finger runs down the jugular groove.



FIGURE 24-12 Two-handed thyroid palpation technique: A helper (possibly cat's owner) elevates the cat's chin to extend the neck. The clinician runs both index fingers, on either side of the trachea, from the larynx down to thoracic inlet. The thyroid is circled.

- **Norsworthy technique:** The clinician is positioned directly behind the cat, which is placed in standing position or sternal recumbency. The head of the cat is elevated and turned (45 degrees) alternatively to the right or left, away from the side being assessed (i.e., to palpate the right thyroid lobe, turn the cat's head to the left). The clinician's index finger is placed in the groove formed by the trachea and sternothyroid muscle just below the larynx and then moved downward in the groove to the thoracic inlet (Figure 24-11). If the thyroid lobe is enlarged, a characteristic "blip" is felt as the index finger passes the goiter.⁷⁷
- **Two-handed technique:** The clinician is placed behind the sitting cat. A helper (which can be the cat's owner) elevates the cat's chin to extend the neck. The clinician runs both index fingers, on either side of the trachea, from the larynx down to thoracic inlet (Figure 24-12). As with the other techniques, a "blip" is felt as the index finger passes the goiter. This technique allows bilateral assessment with fingers of similar sensitivity.

The Norsworthy and classic techniques were compared, and both techniques were found to have a very good within- and good between-examiner agreement.

The classic technique proved to be slightly more sensitive and specific in this study, but the authors were more familiar with it.⁸¹ In one author's (RMB) practice, multiple techniques are used, and it seems that some thyroids that are more subtle to palpate are more noticeable with different techniques in different cats. All practitioners should be encouraged to practice all three techniques routinely.

Hyperactivity, Behavioral Changes, and General Appearance

The hyperactivity shown by hyperthyroid cats can be misconstrued by their owners as a sign of healthiness. In many cases the veterinarian may need to explain that older cats are usually quite sedentary and the increased activity is a manifestation of underlying processes causing agitation. Anxiety and restlessness can be obvious to owners if the cat yowls; the major differential diagnoses for night yowling are hyperthyroidism and hypertension (or both) as well as cognitive dysfunction. In clinical practice the restlessness shown may be manifested as an impaired tolerance for restraint for blood sampling (for example).

The hair coat of hyperthyroid cats is often dull and may be matted. Many hyperthyroid cats groom obsessively, resulting in alopecia and even miliary dermatitis; this may be associated with an underlying allergy (e.g., flea allergy dermatitis), but the response is magnified by apparent obsessive-compulsive behavior.

The increased activity in generally thin cats with dull coats has led to the description of hyperthyroid cats as “acting like they are alive, looking like they are dead.”

Gastrointestinal Signs

Aside from weight loss, usually seen with increased or stable appetite, many hyperthyroid cats show other gastrointestinal signs, such as vomiting and diarrhea. Vomiting may be associated with rapid overeating; diarrhea is most likely due to intestinal hypermotility, although malabsorption is also a factor.

Urinary Signs

Polyuria and polydipsia are frequent signs of hyperthyroidism.¹³ Thyroid hormones have a diuretic action that was recognized in the 1930s and 1940s,¹⁰⁴ and so hyperthyroidism (with renal disease and DM) is one of the three major rule-outs for a cat presenting with polyuria and polydipsia. Of course, conditions can occur concurrently, and diagnosing renal disease with hyperthyroidism may be difficult, insofar as hyperthyroidism can mask underlying renal disease.^{8,38,133} Lower urinary tract signs may also be seen in hyperthyroid cats; a recent study demonstrated urinary tract infection in 12% of hyperthyroid cats assessed,⁶⁶ and one of the authors (RMB) has recognized noninfectious hematuria and dysuria in hyperthyroid cats that resolve on management of the hyperthyroidism.

Apathetic Hyperthyroidism

A percentage of hyperthyroid cats show atypical signs in which hyperexcitability or restlessness is replaced by depression or weakness. Although weight loss is present in these cats, it is accompanied by anorexia instead of increased appetite. Most studies have recognized these atypical signs in 5% to 10% of hyperthyroid cats,^{13,123} but one (smaller) study found 20% of hyperthyroid cats to be lethargic and 28% to be inappetent.¹⁴ Along these lines, although cardiac changes in hyperthyroid cats usually result in tachycardia, right bundle branch block and incomplete atrioventricular block, resulting in bradycardia, have been observed.³⁴ These disparate signs emphasize the need for clinicians to have a high index of suspicion for this common disease.

Diagnosis

The diagnosis of hyperthyroidism is usually straightforward, insofar as 90% of hyperthyroid cats have an elevated serum total T₄.¹⁰⁰ However, screening plasma (or serum) biochemistry and hematology are important to assess concurrent conditions that may affect the management if hyperthyroidism is diagnosed, as well as provide baseline values for parameters that can be affected by treatment (e.g., urea and creatinine or leukocytes). Thorough screening tests also aid in diagnosis if a cat with

typical clinical signs of hyperthyroidism is not, in fact, hyperthyroid.

Hematologic Findings

Hematologic findings are usually nonspecific and mostly not clinically important. However, it is important to note baseline hematologic values because hematologic adverse reactions are possible when treating hyperthyroid cats with methimazole or carbimazole.^{73,99} Some studies have found erythrocytosis and macrocytosis in approximately 50% of cats,^{13,98} thought to be associated with direct bone marrow effects of thyroid hormones. Stress leukograms are sometimes recognized; eosinophilia and lymphocytosis have also been described.^{13,98,123}

Biochemistry Findings

The liver enzymes, ALT, ALP, lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) are increased in most hyperthyroid cats.^{13,98,123} These liver enzyme changes and total T₄ concentrations are significantly correlated.^{33,73} Despite sometimes very high increases, histologic examination of the liver usually reveals only mild, nonspecific changes. Liver enzymes return to normal on successful treatment of hyperthyroidism.⁷³

Concurrent renal disease is common in hyperthyroid cats; however, the diagnosis of renal disease in hyperthyroid cats is not necessarily straightforward because of the interactions between the two diseases.* Blood urea nitrogen (BUN or urea) can be elevated in hyperthyroid cats as a result of excessive protein catabolism³⁷ but can also be decreased as a result of the increase in glomerular filtration rate (GFR) that occurs in hyperthyroidism.¹⁵ Creatinine is usually reduced in hyperthyroid cats because of both increased GFR and reduced muscle mass.¹³³ One study found that most cats that have concurrent (masked) renal disease have urine specific gravities (USGs) that are below 1.040.¹³⁶ However, another study found that some cats with renal disease unmasked after treatment of hyperthyroidism had pretreatment USGs that were above 1.040, which suggests that USG cannot always predict concurrent renal disease.¹⁰⁸ Predicting which hyperthyroid cats will develop overt azotemia after treatment of hyperthyroidism can be difficult to impossible. The determination of GFR is clearly the best predictor of posttreatment chronic renal disease (CRD), with a low to low-normal GFR indicating that a hyperthyroid cat is at increased risk for posttreatment azotemia. However, techniques for assessment of GFR are not widely used in practice, and even GFR determinations are not a 100% perfect predictor of CRD. Routine pretreatment parameters such as serum urea or creatinine concentrations and

*References 1, 5, 38, 133, 135, 137.

USG are certainly useful, but they cannot consistently predict impending azotemia.¹⁰⁸ Similarly, treatment trials with methimazole or carbimazole can be very useful in unmasking concurrent renal disease, but these evaluations are not perfect predictors of CRD either. The interactions between CRD and hyperthyroidism are covered in more depth in Chapter 35.

Should methimazole trials be performed in all hyperthyroid cats? Again, determining which untreated hyperthyroid cats have clinically significant underlying CRD is sometimes difficult. Use of methimazole or carbimazole can provide a “preview” of how the cat will be after curing hyperthyroidism. Thus many veterinarians attempt trial therapy with methimazole or carbimazole to help test what renal function might remain after treating the hyperthyroidism. If no marked deterioration occurs, then a more permanent therapeutic option for hyperthyroidism may be recommended.

Except for advanced (IRIS Stage 3-4) CRD, the necessity of this approach in cats without pretreatment azotemia is questionable, given that treatment for the hyperthyroidism is required whatever the outcome. In support of this reasoning, the survival of nonazotemic cats that do develop CRD is not shorter than those that do not develop azotemia after treatment of hyperthyroidism. In one study the medium survival time of cats that developed azotemia (595 days) was similar to that of cats that remained nonazotemic (584 days) after treatment.¹⁴⁵

Hyperphosphatemia, independent of azotemia, has been recognized in hyperthyroid cats.^{2,4,13,98,123} This, with the recognized increase in the bone isoenzyme of ALP (which contributes to liver enzyme increases) suggests altered bone metabolism. Circulating osteocalcin concentration, a measure of osteoblastic activity and bone remodeling, is increased in hyperthyroid people, and this was recognized in nearly half of hyperthyroid cats in one study.² Coincident with this change, decreased blood ionized calcium and increased parathyroid hormone can be seen. The reasons for these changes are not entirely clear; they may be associated with increased tubular resorption of phosphate together with increased phosphate loads from exaggerated bone resorption and muscle catabolism.⁴

Blood glucose concentrations may be increased in some hyperthyroid cats, in many cases reflecting a stress response; however, hyperthyroidism is also associated with glucose intolerance characterized by delayed clearance of administered glucose from the plasma despite increased secretion of insulin.⁴⁶

Thyroid Function Testing

Serum total T₄ is preferable as a screening test for hyperthyroidism because although total T₃ concentrations are highly correlated to total T₄,^{13,98,100} 25% to 30% of

hyperthyroid cats have serum total T₃ within the reference range.^{13,100}

Most total T₄ assays available have been independently assessed and found to be comparable in ability to diagnose hyperthyroidism. Practitioners should have some awareness of the techniques available and being used by their commercial laboratories (or in house).

- Radioimmunoassay (RIA) validated for feline serum,^{107,124} such as Coat-A-Count Total T₄ (Diagnostic Products Corp), is considered to be the preferred technique.^{54,64,88}
- Chemiluminescent enzyme immunoassays such as Immulite Total T₄ (Diagnostic Products Corp) have also been validated for feline serum.^{54,114} Many commercial laboratories prefer this technique because it is more automated.
- An enzymatic chemistry method (DRI thyroxine assay, Microgenics Corporation) is also now being used by some laboratories. This technique has the advantage for the laboratory of being fully automated, which benefits the practitioner and patient because results are available sooner. However, this technique does not appear to have been independently validated for cats.
- In-house enzyme-linked immunosorbent assay (ELISA) test kits are also available. One study found discrepancies with this in-house testing method compared with RIA,⁶⁴ but two more recent studies have found clinical agreement between the same in-house testing and validated techniques.^{54,85}

Difficulties in Diagnosing Hyperthyroidism

Difficulties arise with the diagnosis of hyperthyroidism when a cat is hyperthyroid but total T₄ is not elevated or a cat has a palpably enlarged thyroid lobe (or both lobes) but does not have functional hyperthyroidism.

Hyperthyroid Cat with Normal T₄

Some cats with overt clinical signs of hyperthyroidism can have normal total T₄ believed to be due to either of the following:

1. Fluctuation of T₄ and T₃ concentrations in and out of the normal range. T₄ and other thyroid hormones have been shown to fluctuate considerably over time in hyperthyroid cats. These fluctuations seem to be relevant only in cats with mild hyperthyroidism in which a fluctuation downward can lower T₄ to within the reference range.⁹⁶
2. Suppression of serum T₄ and T₃ concentrations into the normal range because of concurrent non-thyroidal illness.^{67,95,100} Diseases that suppress T₄ include chronic renal disease, DM, neoplasia, gastrointestinal disorders, and primary hepatic

disease.¹⁰⁰ One of the authors (RMB) has also recognized infection as suppressing T₄, such as that acquired through a cat fight injury or dental disease. In the case of renal disease, hyperthyroidism can mask renal disease concurrent with the renal disease suppressing T₄.^{100,144} Thus cats with mild kidney disease and mild hyperthyroidism may have neither azotemia nor elevated total T₄. Occasionally, hyperthyroid cats that are extremely ill may have clinical signs of hyperthyroidism but serum total T₄ concentrations suppressed to the low end of the normal reference range.^{100,126} In such cases the concurrent illness dictates the prognosis, and the existence of hyperthyroidism is of lesser clinical significance.⁸⁸

Because there is no definitive approach to diagnose hyperthyroidism when total T₄ is normal, the practitioner has several options:

- 1. Repeat total T₄:** When overt, manageable underlying disease, such as a cat fight abscess, is present, this should be managed in the first instance. If signs of hyperthyroidism are recognized when a cat presents for such a problem, the practitioner may elect not to test for hyperthyroidism until after successful treatment. When no overt underlying disease is present, the practitioner should wait at least 1 to 2 weeks because thyroid hormone fluctuations are greater over days than hours.⁹⁶
- 2. Scintigraphy:** Thyroid scintigraphy is a nuclear medicine procedure that produces a visual display of functional thyroid tissue based on the selective uptake of various radionuclides by thyroid tissue. Thyroid scintigraphy is able to identify thyroid disease and define the degree of disease relatively unaffected by the presence of concurrent nonthyroidal illness. Technetium (^{99m}Tc) as pertechnetate (^{99m}TcO₄) is a radioactive iodine isotope that has increased uptake in hyperthyroid cats. The cat is injected intravenously or subcutaneously with pertechnetate, and then images are taken with a gamma camera 20 minutes later. The uptake by the thyroid gland is compared with the uptake by the salivary glands (Figure 24-13). It is generally accepted that the thyroid-to-salivary uptake ratio in healthy cats is less than 1. Scintigraphy is also useful in identifying ectopic thyroid tissue (Figure 24-14), which may be present anywhere from the base of the tongue caudally to within the thoracic cavity.^{11,43,82} Although scintigraphy is highly sensitive in diagnosis of hyperthyroid cats, one study questioned its specificity, with 3 of 14 cats proving to be false positives (by histologic assessment of the thyroids).¹²⁷

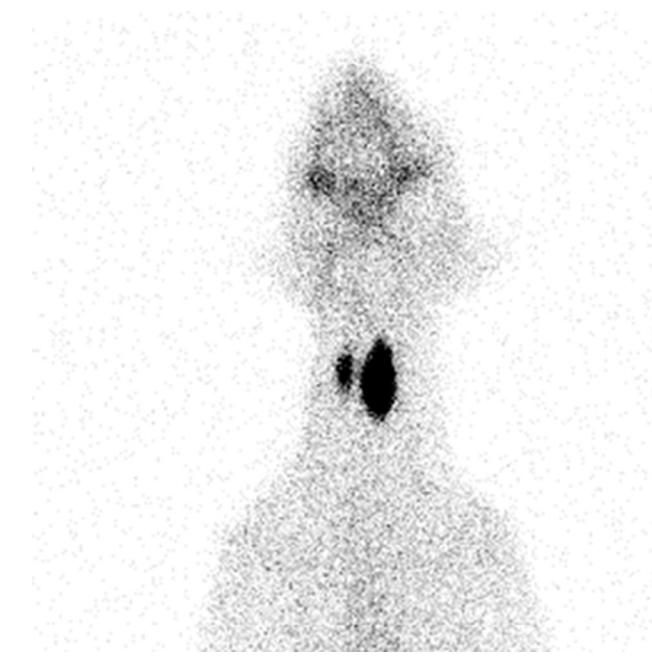


FIGURE 24-13 Scintigraphy indicating bilateral asymmetric pertechnetate uptake by thyroid glands. (Courtesy Dr. Max Zuber, Gladesville Veterinary Hospital, Sydney, Australia.)

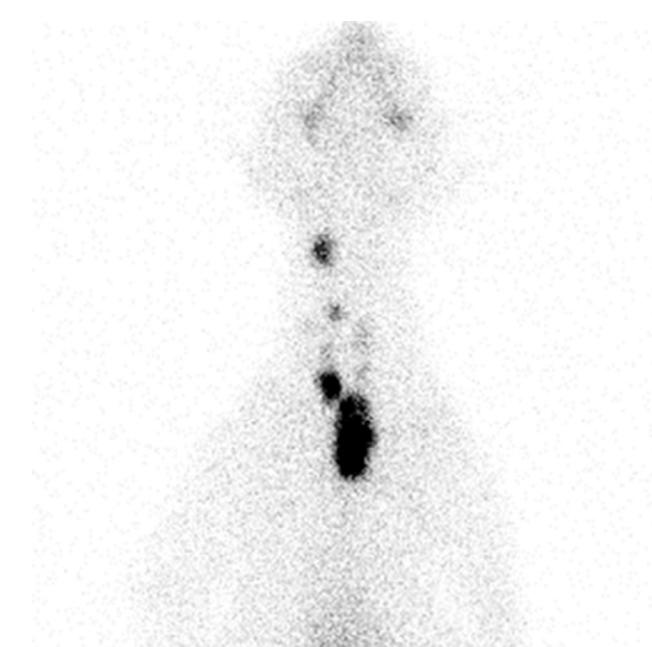


FIGURE 24-14 Scintigraphy indicating pertechnetate uptake ectopically at the thoracic inlet. (Courtesy Dr Max Zuber, Gladesville Veterinary Hospital, Sydney, Australia.)

Methimazole administration may also affect scintigraphy findings, resulting in a significant increase in the percentage uptake of pertechnetate,⁷⁵ although this is not a consistent finding.³⁰

Scintigraphy requires specialized equipment and handling of radioisotopes so is not readily available.

In addition, sedation may be required, especially in fractious cats.

- 3. Free T₄ values (tested by equilibrium dialysis):** The free T₄ value is more sensitive than total T₄ in hyperthyroid cats, with one large study demonstrating 98.5% having elevated free T₄ compared with 91.3% having elevated total T₄.¹⁰⁰ Free T₄ cannot, however, be used as a routine screening test because nonthyroidal disease can cause an elevation of free T₄ in up to 12% of nonhyperthyroid cats.^{72,100} Free T₄ testing provides very useful information when used in conjunction with simultaneous total T₄ testing. A middle to high reference range total T₄ concentration and an elevated free T₄ concentration are consistent with hyperthyroidism.¹⁰⁰ By contrast, a low total T₄ value and elevated free T₄ value are usually associated with nonthyroidal illness.^{72,100} Care must be taken that the laboratory measures free T₄ by equilibrium dialysis, insofar as other techniques are considered less accurate.⁸⁸
- 4. TSH:** As hyperthyroidism develops, TSH is suppressed.^{57,144,146} Theoretically, as in humans, it could be expected that TSH levels should be low in the early stages of hyperthyroidism before T₄ is elevated or that TSH will remain low if T₄ is suppressed by nonthyroidal illness. Although there is currently no feline TSH test, because canine TSH has 96% homology with feline TSH, canine tests have been used.^{36,110,144,146} This is controversial because the canine TSH assays are considered first-generation assays (there are more sophisticated human TSH assays) and normal concentrations cannot reliably be distinguished from undetectable values.²⁹ This claim is supported by one study in which not only all hyperthyroid but also 5 of 40 of

the nonhyperthyroid cats had undetectable levels of TSH.¹⁴⁴ Feline TSH has recently been expressed and purified *in vitro*,¹⁰⁶ and if this work leads to the availability of a feline-specific TSH, this assay may prove useful in diagnosing hyperthyroidism in cats with equivocal T₄ levels.

- 5. Dynamic testing:** In the majority of hyperthyroid cats with normal total T₄ concentrations, identification of concurrent disease, repeat total T₄ analysis, or simultaneous measurement of free T₄ allows confirmation of the diagnosis. Further diagnostic tests are rarely required. Although dynamic thyroid function tests have been recommended in the past as helpful in confirming a diagnosis of hyperthyroidism, the current consensus is that these tests should be considered only in cats with clinical signs suggestive of hyperthyroidism when repeated total T₄ concentration remains within reference range or free T₄ analysis is unavailable or diagnostically unhelpful. The authors rarely, if ever, use these tests. The protocols for these tests are shown in Table 24-6.

- **T₃ suppression:** In a nonhyperthyroid cat, administration of T₃ should suppress TSH secretion and therefore T₄ secretion. In hyperthyroid cats, thyroidal function is autonomous so T₃ administration has little effect on serum T₄ concentration. T₃ (liothyronine, Cytomel, Jones Medical Industries, Pointe Claire, Quebec) must be given orally every 8 hours for seven doses (i.e., over 3 days). Failure to adhere to this protocol means T₃ will not rise and therefore T₄ will not be suppressed.⁹⁷
- **Thyroid releasing hormone (TRH) stimulation:** In clinically normal cats the administration of TRH causes an increase in TSH secretion and serum T₄

TABLE 24-6 Commonly Used Protocols for Dynamic Thyroid Function Tests in Cats⁸⁸

	T ₃ Suppression	TRH Stimulation	TSH Stimulation	
Drug	Liothyronine (Cytomel)	TRH	Bovine TSH	Human TSH
Dose	25 µg every 8 hours for 7 doses	0.1 mg/kg	0.5 IU/kg	0.025-0.20 mg/cat
Route	Oral	Intravenous	Intravenous	Intravenous
Sampling times	0 and 2-4 hours after last dose	0 and 4 hours	0 and 6 hours	1 and 6-8 hours
Assay	Total T ₄ Total T ₃	Total T ₄	Total T ₄	Total T ₄

INTERPRETATION

Euthyroidism	>50% suppression	>60% increase	>100% increase	>100% increase
Hyperthyroidism	<35% suppression	<50% increase	Minimal/no increase	Not determined

TRH, Thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

concentrations, whereas in cats with hyperthyroidism the TSH and serum T₄ response to TRH is blunted or totally absent. T₄ is collected and sampled before and 4 hours after intravenous administration of 0.1 mg/kg TRH. Cats with mild hyperthyroidism show little, if any, rise in serum T₄ values after administration of TRH, whereas a consistent rise in serum T₄ concentrations (approximately a twofold rise) occurs after TRH administration in both clinically normal cats and cats with nonthyroidal disease. Side effects such as salivation, vomiting, tachypnea, and defecation almost invariably occur immediately after administration of the TRH.⁹⁴

- **TSH stimulation:** Exogenous TSH should be a potent stimulator of thyroid hormone secretion; however, serum total T₄ concentrations show little or no increase after exogenous bovine TSH administration in hyperthyroid cats. Recombinant human TSH has been evaluated in healthy cats, and although it appears to be a safe and effective replacement for bovine TSH, it has not yet been evaluated in hyperthyroid cats. TSH stimulation testing is not recommended to diagnose hyperthyroidism.⁸⁸

Enlarged Thyroid Gland But Not Hyperthyroid

Nonfunctional enlargement of thyroid glands (goiter) has been recognized since the 1960s^{61,62} but has taken on new significance since functional hyperthyroidism arose as an entity in the late 1970s.⁹³ Nonfunctional goiter was recognized again in the late 1990s¹⁷ but rose to prominence in 2002.^{76,77} Many authors agree that clinical hyperthyroidism has a prodromal period (also called *subclinical hyperthyroidism* or *prehyperthyroidism*).^{*} One paper claimed to have defined subclinical hyperthyroidism by depressed TSH concentrations,¹⁴⁶ but this has been contested because of the lack of sensitivity of the canine TSH assay.²⁹ It is not clear whether all goiters indicate that the cat will develop hyperthyroidism. Thyroidectomy of nonfunctional goiters has been proposed^{28,76} as a preventive measure. This strategy appears benign,^{28,76} but there is no definitive evidence to support this approach.

Treatment

Medical management with methimazole or carbimazole, surgical thyroidectomy, and radioactive iodine (¹³¹I) are all appropriate modalities to manage hyperthyroid cats. Each has advantages and disadvantages that can be used to integrate them when formulating a treatment plan for each individual hyperthyroid cat. Medical management

is considered reversible, and thyroidectomy and ¹³¹I are considered permanent treatments. Recent studies have indicated that a newly introduced iodine-restricted diet (Hill's Prescription Diet y/d Feline-Thyroid Health) may provide a further option for medical management.^{67b,150}

Treatment Considerations

CONCURRENT CONDITIONS

RENAL Because CRD is very common in older cats, it is hardly surprising that it is commonly found concurrent with hyperthyroidism. As noted in the discussion of diagnosis, the increased GFR and reduced muscle mass that hyperthyroidism induces can mask underlying renal disease.* Because it is not possible to predict which hyperthyroid cats have renal disease, it is ideal to perform a treatment trial of hyperthyroid cats with a reversible therapy (e.g., methimazole, carbimazole) and then reassess renal parameters when rechecking total T₄.³⁷ Because the biggest reductions in GFR occur within the first month and then remain stable for the following 5 months,¹³⁵ a 30-day methimazole–carbimazole trial is appropriate. The practitioner should use discretion to assess whether the cat's hyperthyroidism seems controlled before testing; if, for example, the cat has not gained weight and tachycardia is still apparent, the methimazole–carbimazole dose can be increased and the cat can be tested for T₄ and renal parameters a month later.

If, when T₄ has normalized, renal parameters are normal, planning for a permanent therapy such as thyroidectomy or radioactive iodine can proceed. Mild to moderate kidney disease should not preclude permanent treatment of hyperthyroidism.

Immediate permanent therapy without a methimazole–carbimazole trial is appropriate for relatively young cats with completely normal BUN and creatinine, and USG above 1.035. Moreover, some owners may prefer immediate permanent therapy because of their reluctance to medicate their cat.

Figure 24-15 shows how T₄ is inversely related to urea and creatinine in one particular cat as carbimazole dose was changed over a 40-month period. This case also shows very nicely how the azotemia worsens over time. Although this is likely due to the expected progression of CRD in cats with time, it is important to realize that the hyperthyroid state in itself may be damaging to renal function. Recent research provides evidence that hyperthyroidism may contribute to the development or progression of CRD in cats. First of all, a number of recent reports indicate that many untreated hyperthyroid cats develop proteinuria, which resolves within 4 weeks of

*References 28-29, 76, 77, 140, 141.

*References 1, 5, 37, 38, 133, 135, 137.

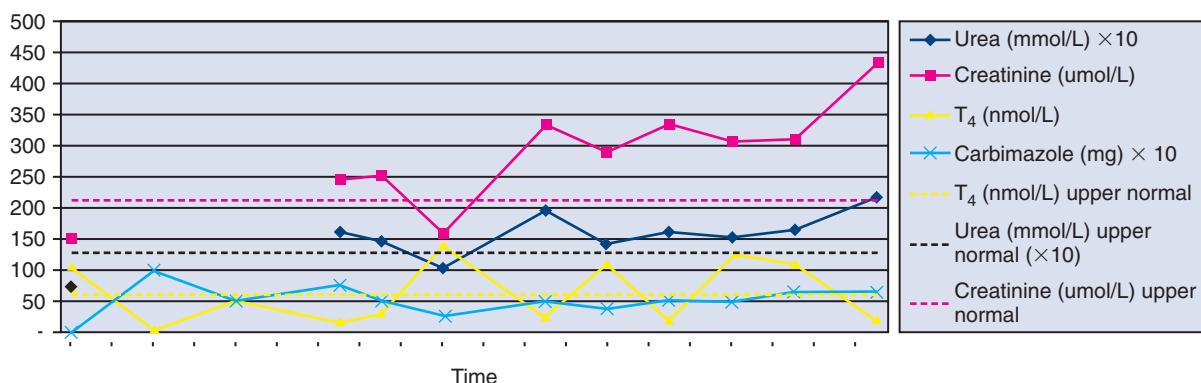


FIGURE 24-15 Variations in T₄ and renal parameters as carbimazole dose was changed multiple times over a 40-month period. The units are shown in the figure key, but more important is the inverse relationship between serum total T₄ (yellow) and renal parameters (creatinine is pink, and urea is dark blue). As carbimazole dose (pale blue) is reduced, T₄ (yellow) elevates and creatinine (pink) and urea (dark blue) decrease. As carbimazole increases, T₄ is suppressed but creatinine and urea increase. The clinical pathology results must be balanced with the cat's clinical responses. A mild elevation of T₄ may be tolerable if there are no cardiac signs and weight loss is not substantial. Conversely, mild azotemia often does not result in clinical signs.

successful treatment.^{136,149} This proteinuria could be a reflection of glomerular hypertension and hyperfiltration, changes in tubular protein handling, or a change in the structure of the glomerular barrier. Secondly, cats with untreated hyperthyroidism have high levels of retinol-binding protein (RBP), a urinary marker for tubular dysfunction or damage.^{134,138} This high urinary RBP excretion may reflect tubular damage or dysfunction resulting from the thyroid-induced hypertrophy and hyperplasia of the tubular cells. After treatment these high urinary RBP levels fall in cats without azotemia but may remain slightly high in cats with preexisting CRD. This too suggests that hyperthyroidism can cause reversible renal dysfunction; however, the renal tubular changes may become irreversible with time as CRD progresses. Thirdly, many cats with untreated hyperthyroidism have high values for urinary N-acetyl-β-D-glucosaminidase (NAG), a lysosomal glycosidase found primarily in epithelial cells of the proximal convoluted tubule.⁶⁰ Like RBP, NAG is a specific marker of active proximal tubular damage. After treatment these high urinary NAG levels decrease, again suggesting that these renal changes can be reversed, at least in cats without preexisting CRD.

Overall, these studies suggest that leaving a hyperthyroid cat untreated (or poorly regulated with methimazole) may be detrimental to long-term kidney function. Treating and curing hyperthyroidism may help both to reverse renal damage and to preserve remaining kidney function.

Concurrent hyperthyroidism and CRD are covered in more detail in Chapter 35.

CARDIAC The cardiac changes for most cats with hyperthyroidism are mild. Murmurs and tachycardia are not often associated with clinical signs of heart disease. However, some hyperthyroid cats initially

present for severe cardiac-related disease. On the occasions when cats show more severe cardiac changes, such as congestive heart failure and aortic thromboembolism, these should be stabilized before a cat undergoes thyroidectomy or is isolated after I¹³¹ therapy.

HYPERTENSION Mild to moderate hypertension appears to develop in approximately 10% to 20% of untreated hyperthyroid cats and is generally reversible on induction of euthyroidism.¹¹⁹ If hypertension is severe or persists after treatment of hyperthyroidism; however, these cats should be managed with amlodipine. In many cases amlodipine can be discontinued when the cat becomes euthyroid. Conversely, some cats are normotensive when hyperthyroidism is diagnosed but may become hypertensive after becoming euthyroid.¹²⁰ In the authors' experience, these cats invariably have some degree of renal disease.

HEPATIC As previously noted, cats often have benign elevations in liver enzymes when diagnosed with hyperthyroidism. Therefore it is not possible to know at the time of diagnosis if increased liver enzymes are due to hepatic pathology unrelated to hyperthyroidism or merely a manifestation of hyperthyroidism. If it is the latter, a treatment trial with methimazole–carbamazole should result in a reduction of liver enzymes, and a permanent treatment should be considered. If, with normalization of T₄, liver enzymes remain elevated, permanent treatment is not ideal and investigations should proceed to diagnose an underlying hepatopathy. However, a reversible hepatopathy can result from methimazole⁹⁹ or carbimazole (not reported except anecdotally, by one of the authors' [RMB] therapy). In this circumstance the practitioner should discontinue medical therapy and, after the cat's recovery, consider whether, on balance, a permanent therapy is appropriate.

OTHER Because hyperthyroid patients are elderly, multiple other concurrent conditions are possible. UTI has been recognized in 12% of hyperthyroid cats⁶⁶ and should be treated before a cat goes into isolation after I¹³¹ therapy.

If, for example, an abdominal mass is recognized at the time of diagnosis, it is not appropriate for a cat to undergo thyroidectomy or I¹³¹ therapy until this has been investigated. Medical therapy is appropriate in this circumstance.

CLIENT CIRCUMSTANCES

Cost of therapy is a major consideration for many clients. Medical therapy costs far less initially. However, the cost of ongoing monitoring can equal that of thyroidectomy or I¹³¹ therapy over a several years. Many (most) cats treated with methimazole or carbimazole are remarkably stable and do not show side effects. All cats should have an initial assessment after 1 month of starting therapy to recheck total T₄, renal parameters, and hematology (and liver enzymes if they were elevated), as well as to assess for weight gain and improvement of any other clinical signs initially shown. Beyond this time cats should be checked every 3 months. It is ideal to recheck total T₄ at each visit, but if the client is concerned about the cost, a thorough physical examination should establish whether the clinical signs of hyperthyroidism are controlled and the testing may be performed less frequently.

Pregnancy and children in the household should be considered and discussed with the client before I¹³¹ therapy because cats will continue to emit radiation for some weeks after returning home. If isolation from pregnant women or children is not possible when the cat returns home, I¹³¹ therapy should not be considered as a treatment option.

Medical Therapy

Methimazole blocks thyroid hormone synthesis by inhibiting thyroid peroxidase, an enzyme involved in the oxidation of iodide to iodine, incorporation of iodine into thyroglobulin, and coupling of tyrosine residues to form T₄ and T₃. Methimazole does not block the release of preformed thyroid hormone, so there is a delay of 2 to 4 weeks before serum T₄ concentrations return to normal after initializing therapy.⁹⁹ Methimazole does not decrease goiter size, and because hyperplasia or adenomatous growth continues, goiters may become larger over time despite therapy. In most cats 2.5 mg twice daily is an appropriate dose to manage clinical signs. In one study of 40 hyperthyroid cats, 5 mg once daily was less effective than 2.5 mg twice daily, with only 54% of cats euthyroid after 2 weeks of once-daily treatment, compared with 87% of cats treated with divided daily dosing.¹²⁹ Doses can be titrated upward if the cat does not respond to the initial dose.

Carbimazole is a derivative of methimazole that is converted to methimazole *in vivo*.⁹⁰ It is available in Australia and Europe. Because a 5-mg carbimazole dose is equivalent to a 3-mg methimazole dose, 5 mg twice daily is an appropriate dose to manage hyperthyroidism in most cats.⁷³ For initial control 5 mg three times daily has been advocated,⁷³ but 5 mg twice daily is adequate in most cats, and if the dose needs to be titrated upward, 7.5 mg twice daily achieves the same result as 5 mg three times daily.

Adverse effects can be seen with both methimazole and carbimazole, although these may be less common and less severe with carbimazole.⁶³ Transient, self-limiting anorexia, vomiting, and lethargy are the most common side effects, occurring in approximately 10% of cats treated with methimazole.⁹⁹ Halving the dose and titrating to the lowest effective dose may be helpful to reduce these side effects.¹³⁰ More serious side effects include blood dyscrasias such as neutropenia and thrombocytopenia in 3% to 9% of treated cats; hepatopathy in approximately 2% of cats^{99,111}; and excoriations of the face and neck in 2% to 3% of cats.⁹⁹ All these adverse effects are reversible on discontinuation of the medication.¹³⁰

Methimazole or carbimazole is adequate to manage 99% of hyperthyroid cats.⁹⁹ Some cats, however, will not tolerate the dose of methimazole or carbimazole necessary to control their hyperthyroidism. In these cases a permanent therapy is recommended. For cats that are not good candidates for permanent therapy (e.g., moderate to severe azotemia, advanced age with other debilitating problems), lower doses of methimazole or carbimazole can be used, and adjunctive medical therapy can be used to manage other problems—for example, a beta blocker such as atenolol to control tachycardia or amlodipine for hypertension. These cats need to be monitored for changes in renal function or continued weight loss.¹³⁰

Transdermal preparations of methimazole^{48,49,111} and, more recently, carbimazole¹⁵ have proved to be effective alternatives to the oral versions of these medications. Transdermal preparations must be prepared by a compounding pharmacy and, to ensure drug stability, should be dispensed in quantities lasting for no more than 1 month. They may be used when the owner has difficulty medicating the cat and may result in reduced gastrointestinal side effects.¹¹¹

Recent studies have indicated that diets with restricted iodine levels (Hill's Prescription Diet y/d Feline-Thyroid Health) can result in normalization of T₄ levels in hyperthyroid cats.^{67b,150} In one study, cats were fed diets with sequentially reduced iodine contents; an iodine restricted food with 0.28 ppm iodine resulted in euthyroidism in 8 of 9 cats and a diet with an iodine content of 0.17 ppm resulted in euthyroidism in all cats tested.^{67b} The one cat that required the lower iodine level for euthyroidism

had a notably higher total T₄ than the other cats tested, suggesting this therapy may be more appropriate for cats with only moderate elevations of T₄. Another study by the same investigators found that a dietary iodine level of 0.32 ppm also resulted in euthyroidism in cats with moderate elevations of T₄ (up to 84 nmol/L [6.5 µg/dL]).¹⁵⁰ Continued control of total T₄ levels was not possible when iodine content was increased to 0.39 ppm.^{67a,67b} These interesting findings may change management of hyperthyroidism in the future. Ironically, a recent publication showed varying levels of available iodine in commercially available foods and suggested that hyperthyroidism in cats may be reduced by providing diets that are adequately supplemented with iodine.^{26b} In humans, it is recognized that both high-iodine^{115a} and low-iodine^{60a} diets can contribute to hyperthyroidism; similar associations in cats are unproven but, if so, restricted dietary iodine therapy would not be expected to be helpful in all hyperthyroid cats. Further, cats with very high total T₄ levels may not be manageable with dietary therapy alone. Additionally, low-iodine diets may increase the percentage uptake of I¹³¹; some authors believe that low-iodine diets in humans can increase radioiodine uptake in thyroid tissue as much as twofold.^{52a} The reduced total I¹³¹ dose required would shorten the necessary hospitalization time after such therapy.

Once euthyroidism has been achieved, it is ideal for the cat to undergo permanent therapy. Thyroidectomy can be performed immediately. Antithyroid drugs appear to interfere with the thyroid's ability to uptake and concentrate radioactive iodine.¹⁰ This is controversial: One study did not find such an association,¹⁸ and another indicated that uptake can be enhanced,⁷⁵ which may create a risk of subsequent hypothyroidism. One recommendation is to discontinue methimazole or carbimazole for at least 1 week before treatment with radio-iodine.⁸⁹ This solution is inappropriate for cats with serious consequences of their hyperthyroidism (e.g., congestive heart failure). These circumstances must be addressed on a case-by-case basis. Cats in these circumstances can continue with medical therapy, undergo thyroidectomy, or proceed with radioiodine therapy (perhaps with less predictable results but without apparent problems in many cases).

Those cats whose owners choose to continue with medical therapy should have ongoing monitoring; every 3 months is an appropriate interval. It is important to assess the cat for clinical signs of hyperthyroidism, but also, ideally, serum total T₄ should be checked. If renal parameters are normal, these need to be checked only every 6 months.

Thyroidectomy

Thyroidectomy is a straightforward procedure that most surgeons can learn relatively quickly. It is ideal to achieve

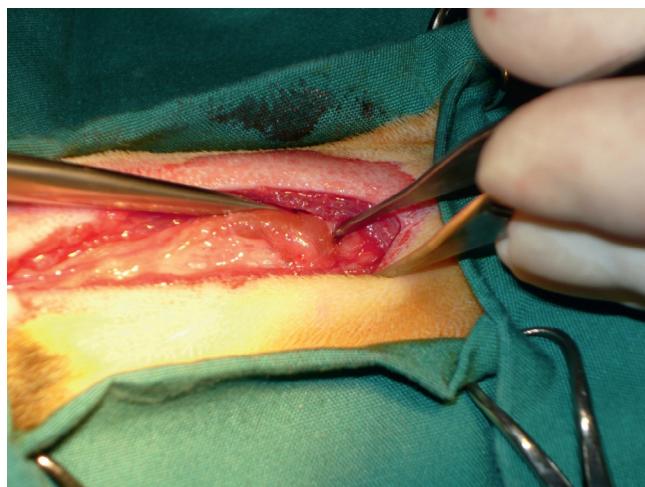


FIGURE 24-16 Thyroidectomy: Blunt dissection is required to free the affected thyroid lobe from surrounding fascia.

euthyroidism before surgery, as already outlined, so the cardiac effects of hyperthyroidism are reduced (and preferably eliminated) to reduce anesthetic risk. The major postsurgical complication is hypocalcemia, which results from damage to the parathyroid glands. To reduce the chances of hypocalcemia, it has been recommended *not* to perform bilateral thyroidectomy but instead to stage surgery and perform surgery on the second side some weeks later.^{31,32} This is not necessary for cats in which one thyroid gland is more prominent. Although disease is bilateral in 70% of cases, one of the authors (RMB) has found that most of these have a dominant side, and it often takes years for hyperthyroidism to recur from the remaining gland, if it does at all. However, the client must be warned that the condition could recur sooner or even immediately.

To further reduce the chances of hypocalcemia, the parathyroid glands should be preserved. This is best achieved by the modified extracapsular technique with parathyroid autotransplantation: After a ventral midline cervical approach, the affected thyroid lobe is dissected free from surrounding fascia, working from caudal to cranial (Figure 24-16). The external parathyroid gland is identified at the cranial aspect of the thyroid gland (Figure 24-17). The thyroid gland capsule is incised adjacent to the parathyroid gland. The parathyroid gland is then carefully separated from the thyroid using sterile cotton-tipped applicators. Once the parathyroid gland is completely separated from the thyroid, the thyroid gland is completely removed, using blunt and sharp dissection and taking care to ligate vasculature. The parathyroid gland is divided with two thirds inserted into a small pocket made in the cervical musculature. Revascularization can occur, and resumption of parathyroid function may result, decreasing the severity and time of postoperative hypocalcemia. Hypocalcemia is a

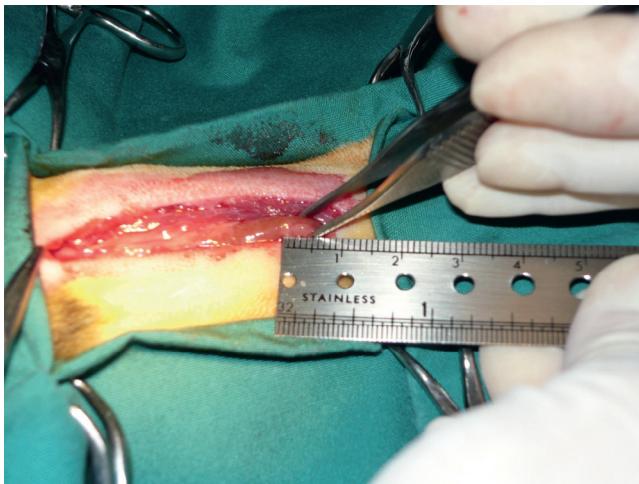


FIGURE 24-17 Identification of the parathyroid while performing thyroidectomy. The parathyroid gland is to the right of the thyroid, just in front of the ruler and measuring approximately 4 to 5 mm. Not all external parathyroids are as easily recognizable as this.

rare consequence of unilateral thyroidectomy. The remaining third of the parathyroid gland is sent for histology with the thyroid gland for confirmation that it is, in fact, parathyroid tissue.⁸⁰ Closure of the incision is by simple continuous suture pattern in the sternohyoideus muscle using absorbable suture, a simple continuous pattern in the subcutaneous tissues with absorbable suture, and interrupted sutures in the skin with nonabsorbable sutures.

Serum total T₄ should be checked 1 month after surgery, again 6 months later, and then annually to check for disease recurrence. The owner should be warned of the possibility of recurrence and return sooner if clinical signs of hyperthyroidism return.

Radioactive Iodine (I¹³¹)

Radioactive iodine (I¹³¹) therapy is considered the gold-standard treatment of hyperthyroidism in cats. Treatment involves either oral dosing or subcutaneous injection and is without associated morbidity or mortality. A single treatment restores euthyroidism in most cats with hyperthyroidism. Although therapy is simple and relatively stress-free for cats, it does require special licensing and hospitalization facilities and extensive compliance with local and state radiation safety laws. The administered radioactive iodine concentrates in and destroys hyperactive thyroid tissue within the cat's body, whether in the normal cervical area or in ectopic sites. The major drawback is that after administration of radioactive iodine, the cat must be kept hospitalized for a period (7 to 10 days in most treatment centers), and visiting is not allowed. Most cats are very settled during their stay after (I¹³¹) therapy (Figures 24-18 and 24-19). Some cats do become depressed with the long isolation, and, more importantly, the isolation period is not appropriate



FIGURE 24-18 After administration of radioiodine, the cat must be kept hospitalized for 7 to 10 days and visiting is not allowed.



FIGURE 24-19 Environmental enrichment helps most cats feel content and settled during their stay.

for cats with any concurrent condition. Less than 5% do not respond adequately to a single treatment; most of these cases respond well to a repeat treatment with resolution of their hyperthyroidism.

Thyrocytes do not differentiate between stable and radioactive iodine; therefore radioiodine, like stable iodine, is concentrated by the thyroid gland after administration.^{12,44,92} In cats with hyperthyroidism, radioiodine is concentrated primarily in the hyperplastic or neoplastic thyroid cells, where it irradiates and destroys the hyperfunctioning tissue.^{91,92} Normal thyroid tissue, however, tends to be protected from the effects of radioiodine because the uninvolved thyroid tissue is suppressed and receives only a small dose of radiation (unless very large doses are administered).

When administered to a cat with hyperthyroidism, a large percentage of radioiodine accumulates in the thyroid gland (i.e., most cats extract between 20% and 60% of the administered radioiodine dose from the circulation).^{12,44} The remainder of the administered I¹³¹ is excreted primarily in the urine and, to a lesser degree,

the feces.^{12,44} I¹³¹ has a half-life of 8 days and emits both beta particles and gamma radiation. The beta particles, which cause 80% of the tissue damage, travel a maximum of 2 mm in tissue and have an average path length of 400 µm. Therefore, beta particles are locally destructive but spare adjacent hypoplastic thyroid tissue, parathyroid glands, and other cervical structures.⁸⁹

There is no definitive method to determine the most appropriate dose of I¹³¹. Fixed doses are not recommended because they can provide too low a dose and not adequately treat the disease or they can provide too high a dose, resulting not only in hypothyroidism but also in a greater radiation hazard than is necessary for veterinary staff attending the cat in hospital. A more precise dose can be estimated by scoring systems that take into account the severity of clinical signs, the degree of elevation of T₄, and the size of the palpable gland.^{71,92} Yet more precision can be gained with scintigraphy because it can also recognize ectopic thyroid tissue.

While hospitalized, cats should be housed in cages that shield radiation emission and allow safe collection of urine and feces. The ward should be restricted to staff properly trained in radiation safety. Proper attention cannot be given to cats that become unwell, and samples (e.g., blood, urine) cannot safely be submitted to laboratories. The cat's level of radiation emission must be assessed (usually by Geiger counter) before the cat can be discharged from hospital. Even when home, the cat continues to emit minimal residual radiation for several weeks; therefore close contact with owners should be limited to periods not exceeding 30 minutes and soiled cat litter should be discarded in sanitary sewer systems for about 2 weeks. Contact with pregnant women or children is entirely prohibited in this time.

The most notable side effect of radioactive iodine is hypothyroidism induced by too large a dose. In many cases there may be a laboratory decrease in serum T₄ without clinical signs.

Serum total T₄ should be rechecked 1 month after therapy, although it can take several more months for clinical signs of hyperthyroidism to resolve entirely. Relapse after I¹³¹ is possible but rare, and if it does occur may be 3 or more years after treatment; because of this possibility, rechecking serum total T₄ annually is ideal.⁹²

Diagnosis and Treatment of Thyroid Adenocarcinoma

In most cases, cats with thyroid adenocarcinoma present similarly to those with hyperthyroidism as a result of adenomatous hyperplasia or thyroid adenoma.^{40,45,131}

Histopathologic evaluation is generally considered the gold standard for the diagnosis of thyroid carcinoma, and definitive identification of thyroid

carcinoma on histopathology often requires identification of vascular or capsular invasion and frequently necessitates that excisional biopsy be performed.¹¹ Scintigraphy can be used adjunctively, especially in recognizing regional and distance metastasis,¹¹ but scintigraphy alone cannot reliably distinguish whether the thyroid tissue is malignant.⁴⁵

Thyroid carcinoma may be suspected if the palpable goiter is particularly big, serum total T₄ is particularly high (the authors have seen values greater than eight times the upper limit of normal), or hyperthyroidism persists despite high doses of methimazole or carbimazole. In some cases none of these criteria will apply, and each of these criteria may also apply to benign hyperthyroidism. Failure of a routine treatment approach (e.g., routine doses of methimazole, carbimazole, or I¹³¹) should alert the clinician to the possibility of malignancy. In these circumstances thyroidectomy is recommended so that a histologic diagnosis can be achieved. Some thyroid carcinomas are highly vascular, and excision may be difficult without a high risk of hemorrhage; in these cases a biopsy sample should be taken for diagnostic purposes only.

Thyroid carcinomas sometimes concentrate and retain iodine less efficiently than thyroid adenomas (adenomatous hyperplasia), and the size of carcinomas is usually much larger; therefore extremely high doses of radioiodine are almost always needed for destruction of all malignant tissue.⁴⁰ The combination of surgical debulking followed by administration of high-dose radioactive iodine is the treatment of choice for thyroid carcinoma in humans^{42,50,51} and also has been reported to be successful in cats with thyroid carcinoma.^{40,45,92} If surgical debulking is not possible, higher doses of I¹³¹ will be needed, necessitating a longer hospital stay and a greater risk of subsequent hypothyroidism.

HYPOTHYROIDISM

In cats, as in other species, hypothyroidism is the clinical syndrome that results from the chronic deficient secretion of the two thyroid hormones: thyroxine (T₄) and triiodothyronine (T₃). This syndrome rarely develops spontaneously. Most commonly, feline hypothyroidism is iatrogenic, secondary to overtreatment of hyperthyroidism.

Causes of Hypothyroidism

Adult-Onset (Spontaneous) Hypothyroidism

Surveys of the histologic evaluation of the feline thyroid gland have revealed several pathologic abnormalities consistent with hypothyroidism (thyroid atrophy, lymphocytic thyroiditis, and goiter).^{16,19,62} However, there are

only two well-documented reports of adult cats with spontaneous primary hypothyroidism. In the first cat thyroid biopsy identified a marked lymphocytic infiltrate, consistent with lymphocytic thyroiditis.¹⁰⁵ The second cat had idiopathic atrophy of the thyroid gland.⁷

There are no reports of cats with naturally occurring secondary or tertiary hypothyroidism. One report describes a cat with secondary hypothyroidism (i.e., pituitary thyrotropin [TSH] deficiency) secondary to head trauma.⁶⁸

Congenital Hypothyroidism

Congenital primary hypothyroidism is a rare disease, and only a few cases have been described.* A recessive mode of inheritance for the disorder has been reported in a family of Abyssinian cats and a family of Japanese cats.^{52,122} All cases of congenital disease in cats have been primary, (i.e., defect at the level of the thyroid gland). There are no reports of pituitary (secondary) or hypothalamic (tertiary) forms of congenital hypothyroidism in cats.

Although still rare, congenital hypothyroidism develops more commonly than spontaneous hypothyroidism in adult cats. However, its prevalence is likely underestimated. Because most affected kittens die soon after birth, the condition is commonly misdiagnosed.

Congenital primary hypothyroidism can be divided into two main categories: thyroid dyshormonogenesis and thyroid dysgenesis. Thyroid dyshormonogenesis is a defect in any step of iodine uptake or thyroid hormone synthesis. As in all forms of primary hypothyroidism, the low circulating T₄ concentrations lead to increased pituitary TSH secretion. Because the thyroid follicles remain intact in cats with thyroid dyshormonogenesis, the high circulating TSH concentrations induce hyperplasia of the thyroid gland. Therefore the veterinarian can sometimes palpate an enlarged thyroid gland (bilateral goiter) in cats with this type of congenital hypothyroidism.^{3,52,103,115}

Thyroid dysgenesis is a developmental defect of the thyroid gland, sometimes resulting from TSH receptor abnormalities. Opposite to dysmorphogenesis, thyroid dysgenesis leads to hypoplasia or aplasia of the thyroid gland; this is a nongoitrous form of congenital hypothyroidism.^{101,122,128}

Iatrogenic Hypothyroidism

Iatrogenic hypothyroidism is a well-recognized side effect of treating hyperthyroidism, and it is the most common form of hypothyroidism diagnosed in cats.^{87,101} Any of the treatment options for hyperthyroid cats, including antithyroid drugs, surgical thyroidectomy, and I¹³¹, can potentially produce hypothyroidism.

Although cats treated with methimazole or carbimazole frequently develop a subnormal serum T₄ concentration, they generally do not develop clinical signs associated with hypothyroidism.^{73,99} In such cats the corresponding serum T₃ concentration tends to remain within the reference range. This may explain why these cats generally remain clinically euthyroid. However, cats can develop clinical hypothyroidism with a prolonged overdose of an antithyroid drug.

Most cats will develop hypothyroidism a few days after surgical thyroidectomy. Supplementing with levothyroxine (L-T₄) for a few weeks to months postoperatively can sometimes be beneficial. Even after bilateral thyroidectomy, iatrogenic hypothyroidism is generally temporary, usually resolving within 6 months.¹⁴⁷ Thyroid hormone replacement can then be stopped.

Up to 30% of hyperthyroid cats treated with I¹³¹ are reported to develop iatrogenic hypothyroidism.⁷⁸ However, this prevalence appears greatly overestimated because most cats were diagnosed by a low serum T₄ concentration alone; they did not usually show the clinical features of hypothyroidism.¹⁰⁹ In other reports individualized radioiodine dosing methods reduced the prevalence of permanent iatrogenic hypothyroidism to less than 5%.⁹²

Clinical Features of Hypothyroidism

Although many of the signs that develop in hypothyroid cats are similar to those seen in dogs with the disorder, there are a few major differences.^{22,39} First, hypothyroid cats rarely develop total alopecia, a common sign in dogs. Second, cats may develop a poor appetite, a sign also not reported in hypothyroid dogs. Profound lethargy and mental dullness develops in some cats. Other cats, especially kittens with congenital hypothyroidism, may present with severe constipation as a primary complaint.

Adult-Onset (Spontaneous) and Iatrogenic Hypothyroidism

The major clinical signs of hypothyroidism in adult cats include progressive lethargy, dullness, decreased appetite, and dermatologic changes.^{22,39,87,101} Weight gain, hypothermia, and bradycardia are less common (Table 24-7).

Common dermatologic signs include nonpruritic seborrhea sicca; a dull, dry hair coat; and matting of hair on the back caused by lack of grooming. Hair is easily epilated and regrows poorly after clipping. Some cats will develop alopecia of the pinnae. One cat with spontaneous hypothyroidism developed myxedema. Although obesity may develop, it is not a consistent sign. The cats that do become obese usually have iatrogenic hypothyroidism.^{22,87,101}

*References 3, 21, 52, 101, 103, 115, 121, 122, 125, 128.

TABLE 24-7 Clinical Features of Iatrogenic, Congenital, and Adult-Onset (Spontaneous) Hypothyroidism in Cats

	Iatrogenic	Congenital	Adult Onset
Lethargy	+	+++	++
Dermatologic signs	+	+	++
Weight gain or obesity	++	+	+
Poor appetite	+	+	++
Constipation	+	+++	+
Goiter	- or +	- or +++	-
Disproportionate dwarfism	-	+	-
Delayed closure of growth plates	-	+	-

(+) Present; (-) absent.

Congenital Hypothyroidism

Thyroid hormones affect the function of all organs and are essential for normal growth, skeletal maturation, and brain development. Therefore congenital hypothyroidism is characterized by disproportionate dwarfism and neurologic abnormalities (see Table 24-7).^{*} Hypothyroid kittens develop many signs similar to those observed in adult cats.

The clinical signs of congenital hypothyroidism vary in severity depending on the nature of the defect. Severely affected, untreated kittens rarely survive beyond 16 weeks of age.¹²² At birth the kittens usually appear normal but exhibit retarded growth by 4 to 6 weeks of age. These kittens typically develop signs of disproportionate dwarfism, which is characterized by an enlarged, broad head and short neck and limbs, over the next few months.

Most hypothyroid kittens have severe lethargy and mental dullness, in part because their brain does not develop properly. Left untreated, human babies with congenital hypothyroidism can develop mental retardation. Similarly, some of these hypothyroid kittens are definitively mentally deficient.

On physical examination the veterinarian may detect hypothermia, bradycardia, or palpable goiter (with thyroid dyshormonogenesis).[†] Many kittens suffer from severe, recurrent episodes of constipation. Hair is usually present all over the body, but it consists mainly of undercoat with primary guard hairs

scattered throughout. Unlike adult cats with iatrogenic hypothyroidism, hypothyroid kittens are generally not obese. They may exhibit weight loss, particularly if constipated. Eruption of the permanent teeth may be delayed.

Survival of untreated hypothyroid kittens varies. Many affected kittens die undiagnosed as part of the "fading kitten" syndrome. However, other kittens with milder degrees of goitrous hypothyroidism have clinical signs that partially resolve as they grow to adulthood.⁵² It is thought that their enlarging goiter compensates for the deficient thyroid function in order to achieve a euthyroid state.

Diagnosing Hypothyroidism

Diagnosing feline hypothyroidism can be challenging, regardless of its etiology. A presumptive diagnosis is based on a combination of the history, clinical signs, physical examination findings, and routine laboratory tests. The veterinarian can confirm the diagnosis by use of thyroid function testing or by thyroid imaging techniques.

Diagnosing iatrogenic hypothyroidism in cats starts with determining if the cat has a history of treatment for hyperthyroidism, especially with radioiodine or surgical thyroidectomy. However, a number of factors can make the diagnosis of hypothyroidism difficult to confirm. First, the concomitant presence of another disease (e.g., CRD) in these middle-aged to geriatric cats is common. These concurrent diseases can result in euthyroid sick syndrome, which is characterized by falsely low serum thyroid hormone concentrations. Second, the veterinarian should expect weight gain and a decreasing activity level after successfully treating a cat with hyperthyroidism. Therefore the clinical signs of iatrogenic hypothyroidism and the expected return to a euthyroid status can overlap. Finally, many cats develop a marked transient decrease in total T₄, within the first month of therapy with I¹³¹. This transient hypothyroid state is followed by a return to euthyroidism over the next 3 to 6 months as the remaining normal thyroid tissue recovers and starts to function once again.⁹²

For most cats veterinarians are advised to wait 3 months before making a definitive diagnosis of iatrogenic hypothyroidism after I¹³¹ treatment, especially if the cat is not presenting with the clinical features of hypothyroidism. However, the veterinarian should diagnose or exclude hypothyroidism as soon as possible in cats with renal disease because hypothyroidism, treatment for hyperthyroidism, and chronic renal disease all lower the GFR.^{25,83} The combined effect of these three factors can lead to severe azotemia or even total renal failure. Treating the hypothyroidism can raise the GFR to an acceptable level.³⁵

*References 3, 21, 52, 101, 103, 115, 121, 122, 125, 128.

†References 3, 21, 52, 101, 103, 115, 121, 122, 125, 128.

Routine Hematology, Chemistry Panel, and Urinalysis

The most important reason to perform a routine panel in all cats with suspected hypothyroidism is to exclude nonthyroidal illness. In adult cats with hypothyroidism (both spontaneous and iatrogenic), mild normochromic, normocytic anemia and hypercholesterolemia are the most common routine laboratory findings. Unfortunately, these changes are inconsistent, especially in kittens with congenital hypothyroidism.

Serum Thyroxine Concentration

By definition, cats with hypothyroidism have deficient thyroid hormone secretion. Therefore finding a low serum T₄ concentration is key in diagnosing feline hypothyroidism. A normal T₄ concentration virtually excludes hypothyroidism.

Although important, a subnormal T₄ concentration alone is not definitive. The serum T₄ concentration can also be low in cats with nonthyroidal illness, such as DM, hepatic disease, renal disease, and systemic neoplasia.^{86,95} In general, the severity of the illness correlates inversely with the serum T₄ concentration (i.e., sicker cats have lower serum T₄ concentrations). Because multiple diseases and other factors can falsely lower the serum T₄ concentration in cats, the veterinarian must first rule out nonthyroidal disease before considering a diagnosis of hypothyroidism.

Cats with suspected hypothyroidism and a low T₄ concentration still require additional testing before the veterinarian can make a definitive diagnosis. Further tests such as serum free T₄ (FT₄) concentration, canine TSH (cTSH) concentration, recombinant human TSH (rhTSH) stimulation test, or thyroid scintigraphy are indicated to confirm the disease.

Serum Free Thyroxine (FT₄) Concentration

Free T₄ (FT₄) is the nonprotein-bound fraction of circulating T₄ that can enter cells, producing the biologic effect of thyroid hormone and regulating the pituitary feedback mechanism. FT₄ accounts for less than 1% of circulating T₄. Because only the FT₄ is biologically active, measuring free T₄ is a more sensitive test for diagnosing hypothyroidism. In addition, nonthyroidal illness influences FT₄ less than it influences the total T₄.⁸⁶ Therefore FT₄ is better at distinguishing a euthyroid cat with nonthyroidal disease from a hypothyroid cat. However, only FT₄ assays that use equilibrium dialysis appear reliable, and most commercial laboratories measure FT₄ by inferior analog methods.

Although measuring FT₄ concentration by equilibrium dialysis is a more accurate stand-alone test than total T₄ concentration, FT₄ is far from perfect for confirming feline hypothyroidism for three reasons. First, moderate to severe nonthyroidal illness can falsely lower the

FT₄ concentration, although to a lesser degree than seen with total T₄.⁸⁶ Second, up to 15% of cats with nonthyroidal disease develop a falsely high FT₄ concentration, further confusing the interpretation.^{72,86} Finally, the test is approximately twice as expensive in most commercial laboratories as the total T₄.

Serum Thyroid-Stimulating Hormone Concentrations

In dogs with hypothyroidism, a high serum TSH concentration confirms that the disease is primary (located within the thyroid gland). A specific assay for feline TSH is not yet available. However, the commercially available cTSH assay cross-reacts with feline TSH sufficiently to enable its use as a diagnostic test for hypothyroid cats. In one of the reported adult cats with spontaneous hypothyroidism, the serum TSH concentration was high when measured with the cTSH assay.⁷ Similarly, most cats with iatrogenic hypothyroidism will also develop high serum TSH concentration as measured by the cTSH assay.^{22,39}

Normal cats and cats with nonthyroidal illness generally maintain normal values for serum TSH. Therefore the finding of a low total T₄ or FT₄ in combination with a high TSH concentration greatly improves the diagnostic sensitivity for hypothyroidism.

Thyroid-Stimulating Hormone Stimulation Test

The TSH stimulation test provides important information for diagnosing hypothyroidism because it directly tests the thyroid's secretory reserve. In normal cats administering exogenous TSH produces a consistent rise in total serum T₄ concentration. In contrast, hypothyroid cats show little, if any, rise in the low basal total serum T₄ concentrations after TSH stimulation.^{22,39,87} As in dogs with hypothyroidism, the TSH stimulation test appears to be an effective, noninvasive means of confirming the diagnosis in hypothyroid cats.

In the past bovine TSH was the preferred preparation for TSH stimulation testing in cats. However, bovine TSH is no longer available. Recently, a recombinant human TSH (rhTSH) preparation was validated for TSH stimulation testing in cats.^{116,139} The testing protocol involves collecting samples for total serum T₄ concentration before and 6 hours after the intravenous administration of 25 to 200 µg of rhTSH (Thyrogen, Genzyme Corporation). Administering rhTSH to clinically normal cats generally increases the basal total T₄ concentration by at least twofold. Further studies are needed to validate the use of this test for diagnosing feline hypothyroidism, but one would expect that these cats would experience little to no rise in total serum T₄.

The major disadvantage of this test is that rhTSH is extremely expensive. The vial of rhTSH powder is reconstituted with sterile water (900 µg/vial), and the diluted

TSH can be aliquoted into vials and stored frozen for later use in other dogs and cats. Freezing at -20 degrees C maintains the biological activity of rhTSH for up to 12 weeks.²³ Unfortunately, it is unlikely that most hospitals would perform the test often enough to use the entire supply of rhTSH before it expires.

Radiology

Radiography can be a particularly useful aid in diagnosing congenital feline hypothyroidism because retarded skeletal development, particularly epiphyseal dysgenesis of the vertebrae and long bones, is pathognomonic for the disease.³⁹

Thyroid Scintigraphy

Thyroid scintigraphy (thyroid scanning by nuclear imaging) provides valuable information regarding both thyroid anatomy and physiology, and it can play an integral role in the diagnosis and staging of thyroid disease in cats.^{56,101} Thyroid scintigraphy is considered the gold standard for diagnosing mild hyperthyroidism in cats. Although most veterinarians diagnose hypothyroidism with serum thyroid tests, thyroid scanning is a valuable test as well.

To perform thyroid imaging, a small dose of radionuclide (most commonly, technetium-99m; ^{99m}Tc) is administered subcutaneously. The cats are laid on their abdomen (ventral view) or side (lateral view) 20 minutes later, while a gamma camera acquires the thyroid image.

In normal cats the thyroid gland appears as two well-defined, focal (ovoid) areas of radionuclide accumulation in the cranial to middle cervical region. The two thyroid lobes are symmetrical in size and shape and are located side by side. Activity in the normal thyroid closely approximates activity in the salivary glands, with an expected brightness ratio of 1:1.

Thyroid scintigraphy is considered the best imaging technique for dogs with suspected hypothyroidism because it can distinguish between hypothyroid dogs and dogs with a falsely low serum thyroid hormone concentration. In hypothyroid dogs thyroid imaging typically reveals decreased or even absent radionuclide uptake (thyroid gland is not visible on the scan). In contrast, dogs with a falsely low serum thyroid hormone concentration secondary to illness or drug therapy will have a normal thyroid image.

Thyroid scintigraphy is also a powerful tool for diagnosing adult hypothyroid cats (both spontaneous and iatrogenic). As in hypothyroid dogs, thyroid imaging shows minimal to zero uptake of the radionuclide.⁷

Although few studies have been done, thyroid scanning also appears to be helpful for kittens with congenital hypothyroidism because it can distinguish between thyroid dysgenesis and thyroid dyshormonogenesis. A kitten with thyroid dysgenesis will appear similar to a

hypothyroid adult cat or dog—the thyroid should be dim or not visible. Conversely, a kitten with thyroid dyshormonogenesis will have normal to increased uptake of the radionuclide.¹⁰³ Furthermore, thyroid scanning with radioiodine (I^{131}) can help reveal the mechanism of the dyshormonogenesis. For example, a perchlorate discharge test can reveal a defect in iodine organification.^{52,115}

Treating Hypothyroidism

The recommended treatment for feline hypothyroidism is L-T₄, at an initial dose of 10 to 20 µg/kg daily or 100 µg/cat daily. This dose is adjusted as needed on the basis of a cat's clinical response and postpill total serum T₄ concentration. With proper treatment clinical signs of hypothyroidism can be expected to resolve completely in adult cats. In contrast, kittens have a more variable response to treatment. Their prognosis depends on the severity and duration of time that the condition went untreated.

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ADRENAL GLAND DISORDERS

Mark E. Peterson and Randolph M. Baral

HYPERADRENOCORTICISM

Hyperadrenocorticism (Cushing's syndrome) is the constellation of clinical signs resulting from chronic glucocorticoid excess.^{14,17,41} Hyperadrenocorticism can be naturally occurring as a result of primary hyperfunction of either the pituitary or adrenal gland or iatrogenic subsequent to administration of synthetic glucocorticoids. Of naturally occurring disease, pituitary-dependent hyperadrenocorticism is due to excessive secretion of adrenocortotropic hormone (ACTH), from an adenoma arising in the pituitary gland (pars distalis or pars intermedia), which induces bilateral adrenocortical hyperplasia.^{14,29-30,41} A unilateral adenoma or carcinoma of the adrenal cortex secretes excessive cortisol

autonomously, resulting in suppression of pituitary ACTH secretion and atrophy of the contralateral adrenal cortex.

Although naturally occurring hyperadrenocorticism is rare in cats, both pituitary-dependent hyperadrenocorticism and cortisol-secreting adrenal tumors have been well characterized.^{14,17,30,41} Approximately 75% to 80% of cats with hyperadrenocorticism have the pituitary-dependent form of the disorder; the remaining 20% to 25% have unilateral adrenal tumors. Of the cats with functional adrenocortical tumors, approximately two thirds have unilateral adenoma; the others have adrenal carcinoma.

Cats tend to be more resistant to the effects of exogenous glucocorticoid excess than dogs, but iatrogenic hyperadrenocorticism is a well-recognized disorder in cats.^{25,26}

Progesterone-secreting adrenal tumors have also been recognized in cats, albeit rarely.^{7,12,32,42,47} Clinical signs are similar to those in cats with cortisol-secreting tumors, but measurement of cortisol precursors is necessary for diagnosis.

Clinical Features

Hyperadrenocorticism is a disease of middle-aged to older cats, with a median age of 10 to 11 years. Most case series of cats with hyperadrenocorticism have shown no sex predilection,^{15,17,18,54} but a slight female sex predilection has been suggested.¹⁴ There is no reported breed predilection.

The most common clinical signs (Table 24-8) associated with hyperadrenocorticism include the following (Figures 24-20 and 24-21):

- Polyuria
- Polydipsia
- Polyphagia
- Pendulous abdomen
- Cutaneous changes

Other signs typical for the disease in dogs, such as bilateral symmetric hair loss, weight gain, and muscle atrophy, can be seen in cats with advanced or long-term untreated hyperadrenocorticism.^{14,17,18,54}

Differences in Clinical Presentation Between Cats and Dogs

Despite the apparent similarity between cats and dogs with hyperadrenocorticism, there are major differences in clinical presentation.

POLYURIA AND POLYDIPSIA

In contrast to dogs with hyperadrenocorticism, the onset of polyuria and polydipsia both in cats treated with large doses of glucocorticoids and in cats that develop naturally occurring hyperadrenocorticism is often delayed;

TABLE 24-8 Clinical Signs and Abnormal Laboratory Findings in Cats with Hyperadrenocorticism

Clinical and Laboratory Findings	Approximate % of Cats
CLINICAL SIGNS	
Polyuria and polydipsia	85-90
Pot-bellied appearance	70-85
Increased appetite	65-75
Unkempt, seborrheic hair coat	60-70
Muscle wasting	60-65
Bilateral symmetric hair thinning or alopecia	40-60
Lethargy	40-60
Insulin resistance (high daily insulin dose)	45-55
Weight loss	50-60
Fragile, tearing skin	30-50
Infection or sepsis	30-40
Obesity or weight gain	20-40
Hepatomegaly	25-35
Calcinosis cutis	0
COMPLETE BLOOD COUNT	
Lymphopenia	60-65
Eosinopenia	55-60
Mature leukocytosis	45-55
Monocytosis	20-25
SERUM BIOCHEMICAL ANALYSIS	
Hyperglycemia	80-90
Hypercholesterolemia	30-45
High alanine aminotransferase activity	35-40
High alkaline phosphatase activity	10-20
URINALYSIS	
Glycosuria	85-90
Urine specific gravity <1.015	5-10
Ketonuria	5-10

polyuria usually coincides with the development of moderate to severe hyperglycemia and glucosuria with subsequent osmotic diuresis.^{14,21,28,41} Therefore these signs are not present in most cats during the less advanced stages of hyperadrenocorticism when glucose tolerance is still normal (i.e., before development of DM).

Although they are rare in cats with hyperadrenocorticism, it is important to realize that polyuria and polydipsia can also develop either without concurrent diabetes or before the progression of overt DM.^{17,54} The



FIGURE 24-20 Cat with hyperadrenocorticism caused by a unilateral adrenal adenoma. Note the unkempt hair coat, pot belly, and alopecia on the ventral abdomen and tail.



FIGURE 24-21 Ventral abdomen of a cat with advanced pituitary-dependent hyperadrenocorticism. Notice the alopecia, prominent abdominal veins, thin skin, and loss of cutaneous elasticity.

mechanism for the development of polyuria and polydipsia in these nondiabetic cats is unclear, but it appears to be related to concurrent renal disease in most.

SKIN FRAGILITY

Up to half of all cats with hyperadrenocorticism develop fragility of the skin, somewhat resembling that seen in cats with cutaneous asthenia (Ehlers–Danlos syndrome).



FIGURE 24-22 Cat with pituitary-dependent hyperadrenocorticism and diabetes mellitus. Note the multiple open wounds on the dorsal back. A large wound above the shoulder has been sutured by the referring veterinarian. This cat did not have alopecia, but the dorsal truncal area was shaved to facilitate treatment. The nonhealing wound is secondary to severe thinning of the skin.

This sign only rarely, if at all, develops in hyperadrenocorticoid dogs.^{10,14,28,41,54} In affected cats the skin tends to tear with routine handling or when the cat plays with other cats, leaving large denuded areas (Figure 24-22). Many of the other cutaneous features of hyperadrenocorticism in cats are similar to those reported in dogs (e.g., unkempt hair coat, bilateral symmetric hair loss, atrophic thin skin, and bruising of the skin), but skin fragility appears to be a unique though serious manifestation of the disease in cats (see Table 24-8).

WEIGHT LOSS

Many cats with hyperadrenocorticism have a history of weight loss rather than weight gain or obesity as is seen in dogs with this disease (see Table 24-8). In most cases this weight loss occurs secondary to poorly controlled DM, which occurs in up to 90% of cats with hyperadrenocorticism. This concurrent diabetes may be slightly *insulin resistant* in some cats, but most are not receiving extremely high doses of insulin. Insulin resistance, even when present, is never as severe as in cats with acromegaly, in which extremely high insulin doses are

sometimes required to control the GH-induced diabetes (see the section on **Pituitary Disorders** in this chapter).

Diagnosis

Routine Laboratory Tests

Routine laboratory results are variable and not necessarily specific for the disease.^{14,17,21,41,54} The classic hematologic changes of mature leucocytosis, eosinopenia, lymphopenia, and monocytosis (see Table 24-8) may be reported, but these findings are inconsistent. By far the most striking serum biochemical abnormality reported is severe hyperglycemia and glycosuria (see Table 24-8). Hypercholesterolemia is seen in about half of affected cats and may be caused, at least in part, by a poorly controlled diabetic state. High serum ALT levels are also seen in a third of affected cats, probably related to the hepatic lipidosis associated with diabetes. In dogs with hyperadrenocorticism, steroid induction of a specific hepatic isoenzyme of ALP causes increases in the serum activity of this enzyme in 85% to 90% of cases; whereas only 10% to 20% of cats with hyperadrenocorticism have high ALP activity (see Table 24-8). The mild increase in serum ALP activity found in some cats probably results from the poorly regulated diabetic state rather than from a direct effect of glucocorticoid excess, insofar as it may normalize with insulin treatment alone, despite progression of the hyperadrenocorticism.

Cats with hyperadrenocorticism usually maintain urine specific gravity above 1.020 in spite of clinical polyuria and polydipsia. The dilute urine concentrations commonly seen in dogs with hyperadrenocorticism are rarely seen in cats. Again, this difference in urine concentration probably reflects the fact that polyuria in most cats is the result of hyperglycemia and glycosuria rather than being a direct inhibitory effect on secretion or action of antidiuretic hormone (ADH), as in dogs.

Pituitary-Adrenal Function Tests

Endocrinologic evaluation of cats suspected of hyperadrenocorticism is a two-step process:

1. Screening tests to confirm the diagnosis
2. Differentiating tests to distinguish pituitary-dependent disease from adrenal tumors

Test results can be difficult to interpret because clinical signs are often less dramatic in cats than in dogs, and results of individual tests are often inconsistent with poor sensitivity or specificity. In many cases it is necessary to use a combination of tests to determine if hyperadrenocorticism is present, as well as to determine the cause of the disorder.

SCREENING TESTS FOR HYPERADRENOCORTICISM

There are three endocrine tests that can be used for diagnosis of cats suspected of hyperadrenocorticism:

1. ACTH response test
2. Urine cortisol:creatinine ratio
3. Low-dose dexamethasone screening test

None of these tests is perfect, and each has its advantages and disadvantages. It is therefore recommended that the diagnosis of hyperadrenocorticism be reserved for cats with clinical signs of the disease, as well as endocrine test results consistent with that diagnosis.

ACTH RESPONSE TEST The ACTH stimulation test is commonly used as a screening test for hyperadrenocorticism in dogs and has also been recommended as a diagnostic test for cats suspected of having hyperadrenocorticism. This is the only test that can be used to distinguish iatrogenic from naturally occurring hyperadrenocorticism; it requires relatively little time (1 hour) and only two venipunctures.

Regardless of the basal cortisol value obtained, diagnosis of naturally occurring hyperadrenocorticism depends on demonstration of a post-ACTH cortisol concentration that is higher than the reference range for post-ACTH cortisol values. In contrast, cats with iatrogenic hyperadrenocorticism would be expected to have a subnormal response to exogenous ACTH administration.

In cats the main problem with the ACTH response test as a screening test for hyperadrenocorticism is poor sensitivity. Only 35% to 50% of cats with naturally occurring hyperadrenocorticism show an exaggerated serum cortisol response, whereas up to two thirds of cats with the disease have "normal" test results. Therefore the ACTH response test is not nearly as useful for detecting naturally occurring hyperadrenocorticism in cats as it is in dogs, where the test sensitivity is approximately 85%. However, if iatrogenic hyperadrenocorticism is suspected, the ACTH response test remains the screening test of choice to document secondary adrenocortical suppression.^{14,17,21}

A variety of chronic illnesses (not associated with hyperadrenocorticism) also appear to influence ACTH-stimulated cortisol secretion in cats.^{41,56} Stress associated with chronic illness most likely results in some degree of bilateral adrenocortical hyperplasia in sick cats, which could account for an exaggerated cortisol response to ACTH. Therefore the diagnosis of hyperadrenocorticism should not be based solely on the results of basal or ACTH-stimulated serum cortisol concentrations but also the cat's history, clinical signs, and routine laboratory findings.

Sex hormone-secreting adrenal tumors have also been rarely recognized in cats.^{7,9,12,32,47} Clinical signs are similar to those in cats with cortisol-secreting tumors but, as in the dog, measurement of cortisol precursors is necessary for diagnosis. In these cats measurement of serum or plasma sex hormones (e.g., progesterone,

17-hydroxyprogesterone, androstenedione, testosterone, estradiol) before and after ACTH stimulation is an aid to diagnosis. However, ACTH stimulation testing is of limited value in diagnosis of these cats because most are found to have high basal serum concentrations of the sex steroid (or steroids), making stimulation tests unnecessary.

One commonly employed protocol for this test (Table 24-9) is to collect blood for determination of serum (or plasma) cortisol concentration before and 60 minutes after administration of 125 µg synthetic ACTH (tetracosactrin or cosyntropin) intravenously.⁴¹ In cats intravenous administration of ACTH induces greater and more prolonged adrenocortical stimulation than the intramuscular route and is therefore preferred.⁴¹ Lower doses of synthetic ACTH (1.25 and 12.5 µg per cat) produce comparable cortisol stimulation.³⁹ However, more prolonged stimulation is attained after administration of higher doses, and doses as high as 250 µg have been recommended for obese cats, particularly if sampling is delayed for any reason.⁴⁸

Overall, the ACTH stimulation test is *not* recommended as the initial screening test for hyperadrenocorticism in cats because of two important reasons: (1) The test lacks sensitivity, and most cats with hyperadrenocorticism will have normal results; and (2) the other two screening tests (urine cortisol: creatinine ratio and low-dose dexamethasone suppression test) are clearly superior tests because of their increased test sensitivity.

URINE CORTISOL:CREATININE RATIO The urine cortisol: creatinine ratio is a valuable, highly sensitive screening test that can be used to help diagnose hyperadrenocorticism in cats.^{17,18} As a diagnostic test, the test sensitivity for the urine cortisol: creatinine ratio ranges from 80% to 90%. However, as with the ACTH response test, the finding of a high (false-positive) urine cortisol: creatinine ratio is common in cats with moderate to severe nonadrenal illness.^{11,20} This is especially true in cats with illnesses that are not usually associated with hyperadrenocorticism.

It is best to have the owner collect the urine specimen from the cat at home and bring the sample to the veterinary clinic for submission to the laboratory (see Table 24-9) to avoid the stress of travel or hospitalization (which could falsely increase the urine cortisol: creatinine ratio). The use of nonabsorbable cat litter or replacement of the cat litter with nonabsorbent aquarium gravel¹⁸ will help owners collect a urine sample from their cats.

Overall, the urine cortisol: creatinine ratio is a sensitive diagnostic test for distinguishing cats with hyperadrenocorticism from those that do not have the disease. However, because the specificity of this test appears to be low, the veterinarian must carefully evaluate the cat's history and results of physical examination when

TABLE 24-9 Diagnostic Tests Used in Cats with Suspected Hyperadrenocorticism

Test	Test Protocol
SCREENING TESTS	
ACTH response test	Collect baseline blood sample for serum cortisol measurement Administer synthetic ACTH (tetracosactrin at 0.125 mg intravenously) Collect post-ACTH sample for cortisol determination 1 hour later
Urine cortisol:creatinine ratio	Owner collects urine specimen from cat at home and brings to veterinary clinic for submission to laboratory
Low-dose dexamethasone suppression test	Collect baseline blood sample for serum cortisol measurement Administer dexamethasone (0.1 mg/kg intravenously) Collect postdexamethasone sample for cortisol determination 4 and 8 hours later
Combined dexamethasone suppression/ACTH response test	Collect baseline blood sample for serum cortisol determination Administer dexamethasone at the dosage of 0.1 mg/kg intravenously Collect blood for postdexamethasone cortisol concentration 4 hours later Immediately after collecting the 4-hour sample, administer synthetic ACTH (tetracosactrin at 0.125 mg intravenously) Collect post-ACTH sample for cortisol determination at 5 hours (1 hour after ACTH administration)
DISCRIMINATION TESTS	
High-dose dexamethasone suppression test (serum cortisol measurements)	Collect baseline blood sample for serum cortisol measurement Administer dexamethasone (1.0 mg/kg intravenously) Collect post-dexamethasone sample for cortisol determination 4 and 8 hours later
High-dose dexamethasone suppression test (urine cortisol:creatinine measurements)	Owner collect urine from cat at home on two consecutive mornings for determination of baseline cortisol:creatinine ratios Owner then administers three oral doses of dexamethasone to the cat at the dosage of 0.1 mg/kg every 8 hours (e.g., 0800, 1600, and 2400 hours) Owner collects urine sample at home for postdexamethasone sample the next morning (e.g., 0800 hours)
Plasma endogenous ACTH concentration	Collect plasma in chilled tube with protease inhibitor added if available Immediately separate and freeze plasma until assayed
Abdominal ultrasonography	Equipment and skilled operator required to perform procedure

ACTH, Adrenocorticotropic hormone.

interpreting the test result. If the results of the urine cortisol:creatinine ratio are suggestive of hyperadrenocorticism and hyperadrenocorticism is strongly suspected clinically, the diagnosis is best confirmed with another follow-up screening test, such as the low-dose dexamethasone suppression test (discussed in the following section).

LOW-DOSE DEXAMETHASONE SUPPRESSION TEST For cats the low-dose (screening) dexamethasone suppression test is performed using a tenfold higher dose of dexamethasone than is required in dogs.^{14,17,21,24,40} Blood samples for serum (or plasma) cortisol determination are collected before and 4 and 8 hours after administration of dexamethasone at an intravenous dose of 0.1 mg/kg (see Table 24-9).

This low-dose (screening) dexamethasone dosage will consistently suppress serum cortisol concentrations to below approximately 40 nmol/L at 4 and 8 hours in healthy cats and in those with nonadrenal illness. Inadequate serum cortisol suppression at both 4 and 8 hours

is diagnostic for hyperadrenocorticism and is found in all cats with cortisol-secreting adrenal tumors. The vast majority of cats with pituitary-dependent hyperadrenocorticism will also fail to suppress serum cortisol concentration at 4 hours or 8 hours.^{14,21,41} Again, this lack of normal serum cortisol suppression is diagnostic for hyperadrenocorticism.

Overall, the low-dose (0.1 mg/kg) dexamethasone suppression test is an excellent screening test, with close to 100% sensitivity and acceptable specificity. Because this test is clearly better than the ACTH stimulation test and has better test specificity than does baseline urine cortisol:creatinine ratios, this is the test of choice for evaluating a cat with suspected hyperadrenocorticism.

COMBINED ACTH RESPONSE/DEXAMETHASONE SUPPRESSION TEST It is possible to combine the ACTH response test and the low-dose (screening) dexamethasone suppression test (0.1 mg/kg) and perform them in a single day, insofar as only three blood samples must be collected over a 5-hour period (see Table 24-9).

To perform the combined test, a baseline blood sample for serum cortisol determination is collected and dexamethasone administered at an intravenous dose of 0.1 mg/kg, with collection of a further blood sample for cortisol measurement 4 hours later. Immediately after the 4-hour blood sample has been taken, synthetic ACTH (tetracosactrin or cosyntropin) is administered at an intravenous dose of 125 µg, and a post-ACTH sample for cortisol determination is collected at 5 hours (1 hour after ACTH administration).

Almost all cats with hyperadrenocorticism fail to show serum cortisol suppression after dexamethasone administration, and up to one half have an exaggerated response to ACTH administration. By contrast, healthy cats and almost all diabetic cats without hyperadrenocorticism exhibit marked serum cortisol suppression after dexamethasone and have a normal cortisol response after ACTH stimulation.^{14,21,41}

Overall, because of the low sensitivity of the ACTH stimulation portion of this test, the combined ACTH response–dexamethasone suppression test is *not* recommended as a screening test for hyperadrenocorticism. Use of the 8-hour dexamethasone suppression test, as previously outlined, is a better diagnostic test for cats with suspected hyperadrenocorticism.

TESTS TO DETERMINE CAUSE OF HYPERADRENOCORTICISM

Once a diagnosis of hyperadrenocorticism has been confirmed, pituitary-dependent must be distinguished from adrenal-dependent (due to adrenocortical tumors) hyperadrenocorticism. This distinction can have important implications in providing the most effective method of management for the disease. An accurate test is therefore required to determine the cause of the cat's hyperadrenocorticism.

Endocrine tests in this category include the high-dose dexamethasone suppression test and endogenous plasma ACTH measurements. Imaging techniques such as abdominal radiography, ultrasonography, CT, and magnetic resonance imaging (MRI) can also be extremely helpful in determining the cause. In addition, it is only possible to detect metastatic lesions from an adrenal carcinoma by use of these imaging techniques, in the absence of adrenal biopsy and histopathology.

HIGH-DOSE DEXAMETHASONE SUPPRESSION TEST (SERUM CORTISOL MEASUREMENTS) To perform a high-dose dexamethasone suppression test in cats, blood is collected for serum (or plasma) cortisol determination before and 4 and 8 hours after the administration of dexamethasone at 1.0 mg/kg intravenously (see Table 24-9). Note that as with the low-dose dexamethasone suppression test, this dose is 10 times higher than is required in dogs.

After administration of high-dose dexamethasone, adequate cortisol suppression is generally defined as a serum cortisol concentration of less than 30 nmol/L or a cortisol concentration of less than 50% of the baseline value at 4 or 8 hours. In cats with functional adrenocortical neoplasia, high-dose dexamethasone never adequately suppresses cortisol concentration, whereas it suppresses serum cortisol concentration in approximately 50% of cats with pituitary-dependent hyperadrenocorticism.^{14,17,41} This is unlike the situation in dogs with pituitary-dependent hyperadrenocorticism, in which 85% will show adequate cortisol suppression after administration of this high dose of dexamethasone.

Overall, this in-hospital, high-dose dexamethasone suppression test is relatively easy to perform. Suppression of serum cortisol concentrations, when demonstrated, is consistent with pituitary-dependent hyperadrenocorticism. Unfortunately, this test cannot reliably determine the cause of the disorder because one half of cats with pituitary-dependent hyperadrenocorticism fail to demonstrate cortisol suppression with this test. In these cases either plasma ACTH should be measured or abdominal ultrasonography should be performed to determine the cause of the hyperadrenocorticism.

HIGH-DOSE DEXAMETHASONE SUPPRESSION TEST (MEASUREMENT OF URINE CORTISOL: CREATININE RATIOS) The protocol for performing this high-dose dexamethasone suppression test, with monitoring of the percentage of suppression of urine cortisol:creatinine ratios, is as follows. Owners collect urine from the cat on two consecutive mornings (e.g., at 0700 to 0800 hours) for determination of baseline cortisol:creatinine ratios. The owners then administer three oral doses of dexamethasone to the cat at the dosage of 0.1 mg/kg every 8 hours. In other words, immediately after collection of the second basal urine sample, the first dexamethasone dose is administered; the second and third doses are administered in the afternoon and evening of the same day, respectively. The third urine sample is collected 8 hours after administration of the final dexamethasone dose, which would be the next morning. Thus for this test urine is collected on three consecutive mornings, and the three dexamethasone doses are all administered on the second day (see Table 24-9).

The finding that the urinary cortisol:creatinine ratio after dexamethasone administration is suppressed by more than 50% of the average basal cortisol:creatinine ratio is diagnostic for pituitary-dependent hyperadrenocorticism. If suppression is less than 50%, no discrimination is possible, as is the case for the standard high-dose dexamethasone suppression test described above.

Approximately 75% of cats with pituitary-dependent hyperadrenocorticism will demonstrate suppression with this at-home, urine high dose dexamethasone suppression test.^{18,30} This makes this test more reliable than the standard high-dose dexamethasone suppression test for distinguishing the cause of hyperadrenocorticism in cats.

Overall, the at-home high-dose dexamethasone suppression test is generally easier to perform and is better at determining the cause of the disorder than the standard in-hospital test. Therefore for those owners who can administer the dexamethasone, this protocol can be recommended both as a screening test (the baseline urine cortisol:creatinine ratios) and discrimination test (postdexamethasone urine cortisol:creatinine ratio).

ENDOGENOUS ACTH DETERMINATIONS In cats with clinical signs and screening test results diagnostic for hyperadrenocorticism, the basal endogenous ACTH concentration is a valuable test for differentiating the origin of disease.^{14,41} The endogenous ACTH concentration is high to high-normal in cats with pituitary-dependent hyperadrenocorticism, whereas the concentration in cats with functional adrenocortical tumors is low to undetectable.

It is important to remember that blood samples for determination of endogenous ACTH concentration must be handled carefully because ACTH can degrade rapidly in plasma after collection. Special handling requirements (see Table 24-9) include the addition of a protease inhibitor (e.g., aprotinin) when blood is collected, rapid separation of plasma, and proper storage temperatures until the assay is performed. Mishandling of samples may result in a falsely low value that could erroneously suggest an adrenal tumor.

DIAGNOSTIC IMAGING

Of the diagnostic imaging modalities, ultrasonographic evaluation of adrenal size and morphology is most commonly used and extremely useful in determining the cause of the hyperadrenocorticism in cats (Figure 24-23). Adrenal glands are relatively easy to identify in cats. In contrast to the dog, in which the left and right adrenal glands differ in shape, in cats both the adrenal glands are oblong and oval to bean shaped.⁵⁷ In cats with hyperadrenocorticism, if both adrenal glands are large or of equal size, the diagnosis is pituitary-dependent hyperadrenocorticism. If, on the other hand, one adrenal gland is large or misshapen and the contralateral adrenal is small or cannot be visualized on ultrasonographic evaluation, a cortisol-secreting adrenal tumor is diagnosed.^{14,17,24,41}

Although a large adrenocortical tumor can sometimes be visualized on abdominal radiographs, radiography is of no value in confirming bilateral adrenocortical

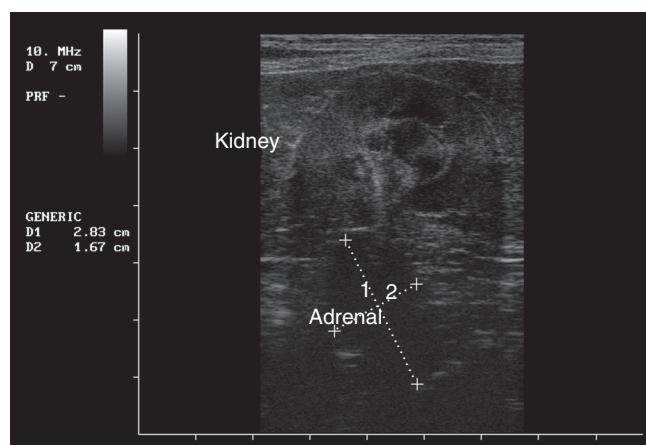


FIGURE 24-23 Ultrasonographic appearance of an enlarged adrenal gland showing proximity to kidney. Note that the adrenal gland appears hypoechoic. The kidney is at an oblique angle and is thus foreshortened.

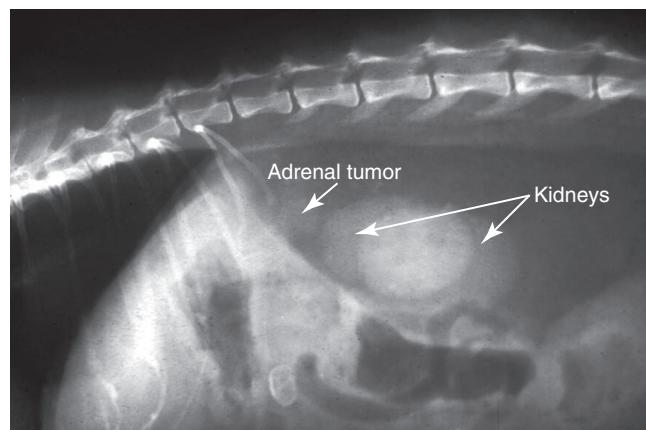


FIGURE 24-24 Lateral abdominal radiograph of a cat with hyperadrenocorticism. Notice the soft tissue mass cranial to the kidneys. Surgical exploration confirmed a right adrenal mass with atrophy of the contralateral left adrenal gland. Histopathology of the adrenal tumor confirmed adrenal adenoma.

hyperplasia in cats with pituitary-dependent hyperadrenocorticism (Figure 24-24). Bilateral calcification of the adrenal gland can occasionally be detected in clinically normal cats, but this should not be interpreted as evidence of an adrenal tumor as it is in dogs.⁴¹

CT and MRI have also proven useful in the detection of pituitary tumors (>3 mm diameter) as well as unilateral adrenal tumors, but both require specialized equipment, are expensive to perform and are not widely available.

Treatment

In cats hyperadrenocorticism is difficult to treat successfully (Table 24-10). From collected experience over the last two decades, adrenalectomy has proved to be the most successful mode of treatment in cats, whereas medical management and use of pituitary radiotherapy

TABLE 24-10 Treatment Options for Cats with Hyperadrenocorticism

Treatment	Indication	Comments
MEDICAL THERAPY		
Mitotane (<i>o,p'</i> -DDD)	PDH or adrenal tumor	Initial dose 25-50 mg/kg daily Drug fails to adequately suppress adrenocortical function in most cats Adverse effects common Not strongly recommended
Ketoconazole	PDH or adrenal tumor	Ineffective in suppressing adrenocortical function in most cats Adverse effects common Not recommended
Metyrapone	PDH or adrenal tumor	Initial dose 250-500 mg daily Potential adverse effects include vomiting and anorexia Beneficial effects on suppressing adrenocortical function may be transient Most useful as preoperative preparation for adrenalectomy Unavailability of drug is a frequent problem
Trilostane	PDH or adrenal tumor	Initial dose 15-30 mg daily; increase to 60-90 mg daily if needed Adverse effects uncommon Effective in suppressing adrenocortical function Useful as preoperative preparation for adrenalectomy and possibly for long-term use Drug licensed for use only in dogs in the United Kingdom (not licensed for use in the United States)
RADIATION THERAPY		
Pituitary cobalt radiation treatment	PDH	Offers a potential cure for pituitary-dependent hyperadrenocorticism May be the only treatment for cats with a large or invasive pituitary tumor Treatment response typically delayed, so use of concurrent medical therapy or bilateral adrenalectomy recommended Limited availability and expense disadvantages
SURGERY		
Unilateral adrenalectomy	Adrenal tumor	Presurgical medical stabilization (e.g., metyrapone, trilostane) helpful Postoperative complications may include pancreatitis and wound dehiscence Clinical signs resolve by 2-4 months postoperatively Glucocorticoid supplementation required for approximately 2 months postoperatively, until function of the atrophied remaining adrenal gland recovers With complete removal of adrenal tumor, cure of disease accomplished
Bilateral adrenalectomy	PDH	Presurgical medical stabilization (e.g., metyrapone, trilostane) helpful Postoperative complications common Clinical signs resolve by 2-4 months postoperatively Lifelong replacement of both mineralocorticoid and glucocorticoid hormones required Pituitary defect (e.g., pituitary adenoma) remains; may later develop pituitary macroadenoma
Hypophysectomy	PDH	Offers potential cure for hyperadrenocorticism Presurgical medical stabilization (e.g., metyrapone, trilostane) helpful Requires highly skilled surgeon and advanced imaging facilities Postoperative complications (diabetes insipidus) common Recurrence of disease possible

PDH, Pituitary dependent hyperadrenocorticism.

have yielded mixed results.* Potential options for medical treatment include the use of the adrenocortico-lytic agent mitotane (*o,p'*-DDD) or drugs that block one or more of the enzymes involved in cortisol synthesis (e.g., ketoconazole, metyrapone, trilostane). The more widespread use of the drug trilostane has resulted in

reasonable medical control for at least a few weeks to months for most cats with hyperadrenocorticism.

Surgical treatment for cats with pituitary-dependent hyperadrenocorticism includes bilateral adrenalectomy or hypophysectomy, whereas unilateral adrenalectomy is indicated in cats with an adrenocortical tumor. Finally, external radiation therapy can also be used for pituitary-dependent hyperadrenocorticism, especially when the cat has a large pituitary adenoma.

*References 10, 14, 15, 33, 34, 41, 49, 54.

Medical Therapy

MITOTANE

Mitotane (*o,p'*-DDD) is an adrenocortical cytolytic agent that has been used extensively for the treatment of hyperadrenocorticism in dogs. Long-term results from a number of different protocols for mitotane treatment of cats with hyperadrenocorticism have been generally discouraging, although limited short-term success is sometimes obtained.^{14,17,41,49} The standard daily dosages of mitotane (25 to 50 mg/kg per day, orally) used for dogs with pituitary-dependent hyperadrenocorticism neither effectively suppresses adrenocortical function nor alleviates clinical signs of the disease, even after prolonged daily treatment periods in most cats.^{14,41} Adverse effects such as anorexia, vomiting, and lethargy are relatively common, even in cats in which the drug has not lowered serum cortisol concentrations (see Table 24-10). Because of the drug's poor effectiveness and high rate of adverse effects, mitotane is not recommended in cats with hyperadrenocorticism.

KETOCONAZOLE

Ketoconazole, a drug used principally for treatment of mycotic disease, inhibits the first step in cortisol biosynthesis (cholesterol side-chain cleavage to pregnenolone) and, to a lesser extent, the conversion of 11-deoxycortisol to cortisol. Although ketoconazole has been used successfully in both humans and dogs with hyperadrenocorticism, the drug does not reliably suppress adrenocortical function in normal cats or cats with hyperadrenocorticism and may cause serious side effects such as thrombocytopenia.^{14,17,41} Therefore ketoconazole cannot be recommended for treatment of cats with hyperadrenocorticism (see Table 24-10).

METYRAPONE

Metyrapone inhibits the action of 11-beta-hydroxylase (the enzyme that converts 11-desoxy-cortisol [11-DOC] to cortisol). It has been used with mixed results in cats with hyperadrenocorticism. Total dosages ranging from 250 to 500 mg per day have been used.^{10,14,33,41} Most cats appear to tolerate the drug reasonably well, but it can induce vomiting and anorexia, necessitating the discontinuation of the drug in some cats (see Table 24-10). If effective, metyrapone reduces both basal and ACTH-stimulated cortisol concentrations and ameliorates the clinical signs of disease. Overall, the effectiveness of metyrapone in cats with hyperadrenocorticism is variable and may be transient, so the drug is best used over the short term to prepare for surgical adrenalectomy. However, metyrapone is difficult to obtain, precluding its widespread use for cats with hyperadrenocorticism.

TRILOSTANE

Trilostane reversibly inhibits the 3-beta-hydroxysteroid dehydrogenase enzyme system in the adrenal cortex, which decreases the synthesis of both glucocorticoids and mineralocorticoids. Trilostane is an effective medical treatment for dogs with hyperadrenocorticism, and experience collected over the last few years indicates that it is also a valuable treatment for cats with the disorder (see Table 24-10).

Thus far, trilostane treatment has been reported in seven cats with hyperadrenocorticism (six with pituitary-dependent disease and one with an adrenal tumor), using a daily dose of 4.2 to 13.6 mg/kg.^{6,34,51} Clinical signs of hyperadrenocorticism resolved to varying degrees after trilostane administration in all these cats.

Based on both the reported studies and personal experience, the recommended starting dose in cats with hyperadrenocorticism is 20 to 30 mg/cat per day, administered once daily or divided at the time of feeding. The daily trilostane dose frequently needs to be adjusted in cats treated with the drug, depending on resolution of clinical signs, serum chemistry results, and repeat ACTH stimulation testing.

Cats on trilostane treatment should be evaluated at 2 weeks, 1 month, 2 to 3 months, and every 1 to 3 months thereafter. At each recheck (scheduled at approximately 3 to 4 hours after the morning trilostane dose was given), the owner should be questioned and the cat examined. Blood is then collected for a hemogram and serum chemistry panel, and an ACTH stimulation test is performed. Although the ideal target range for the post-ACTH cortisol concentration for cats receiving trilostane has yet to be determined, a post-ACTH cortisol concentration of 50 to 150 nmol/L should be the goal. In cats with persistent clinical signs and serum cortisol values higher than this ideal range, the dose of trilostane is increased to 30 to 60 mg/cat per day, administered once daily or divided at the time of feeding. Additional dosage adjustments are made as needed depending on subsequent recheck examinations and ACTH stimulation testing. In some cats daily doses as high as 90 to 120 mg have been needed to control clinical signs and lower ACTH-stimulated cortisol concentrations into the ideal range.

If a cat on trilostane presents with clinical signs consistent with hypocortisolism, trilostane should be stopped and an ACTH stimulation test performed to confirm whether clinical signs are due to low cortisol concentrations. If hypoadrenocorticism is confirmed but serum electrolytes are normal, the veterinarian should stop trilostane and administer glucocorticoids as needed. If hypoadrenocorticism is associated with hyperkalemia or hyponatremia, the veterinarian should discontinue trilostane for 1 month and treat with both glucocorticoids and mineralocorticoids.

Overall, although further investigation is necessary, trilostane appears to be a valuable option for treatment of cats with hyperadrenocorticism and provides a useful medical alternative to metyrapone. Trilostane should be extremely useful in the preoperative preparation of cats with hyperadrenocorticism, before unilateral or bilateral adrenalectomy, but the drug may also be useful as sole agent in the long-term management of some cats.

Radiation Therapy

PITUITARY RADIOTHERAPY

Pituitary-dependent hyperadrenocorticism has been treated with radiation therapy in a number of cats with partial success.^{14,17,27,41,50} Large or invasive pituitary tumors may become smaller, resulting in prolonged survival, and radiotherapy also offers a potential cure for cats with pituitary-dependent hyperadrenocorticism. However, because there is often a delay in reduction in both tumor size and ACTH secretion after therapy, cats can die as a result of complications attributable to hyperadrenocorticism before radiotherapy can adequately control the disease. Veterinarians are therefore recommended to use medical therapy (e.g., trilostane) to help control hyperadrenocorticism before performing radiotherapy in cats with pituitary-dependent hyperadrenocorticism.

Other disadvantages of radiotherapy for treatment of cats with hyperadrenocorticism include its limited availability and high expense, as well as the frequent anesthesia and extended hospitalization periods required to perform the treatment (see Table 24-10). Additionally, some cats require multiple radiation treatments.⁵⁰

Surgery

UNILATERAL AND BILATERAL ADRENALECTOMY

The most successful method of treating cats with hyperadrenocorticism appears to be adrenalectomy (Figure 24-25).*

- Unilateral adrenalectomy should be performed in cats with a unilateral, cortisol-secreting adrenocortical tumor.
- Bilateral adrenalectomy must be performed in cats with pituitary-dependent bilateral adrenocortical hyperplasia.

The chronic hypersecretion of glucocorticoids with hyperadrenocorticism increases the risk of infection and delayed wound healing postoperatively. Postoperative complications also include pancreatitis, thromboembolic phenomena, wound dehiscence, and hypoadrenocorticism. Postoperative outcome is improved with



FIGURE 24-25 Appearance of adrenal cortical adenoma at surgery. Note the large amount of fat present in the surgical field that was present despite the cat being muscle wasted.

presurgical medical stabilization (e.g., trilostane) of cats with severe clinical signs. The clinician must not lose sight of the fact that those cats with pituitary-dependent hyperadrenocorticism undergoing successful bilateral adrenalectomy will still have the pituitary defect (e.g., pituitary adenoma) remaining; these cats may later develop neurologic signs associated with a compressive pituitary tumor.

Unilateral adrenalectomy cases generally require glucocorticoid supplementation for approximately 2 months postoperatively (see Table 24-10), until there is recovery of the glucocorticoid secretory function of the atrophied contralateral adrenal gland. Lifelong replacement of both mineralocorticoid and glucocorticoid hormones is required for cats undergoing bilateral adrenalectomy.

When surgical treatment is successful, resolution of clinical signs (polyuria, polydipsia, polyphagia, lethargy) and physical abnormalities (pot belly, muscle wasting, alopecia, thin skin, hepatomegaly, infection) occurs 2 to 4 months after adrenalectomy.^{15,17,54} In addition, many cats have decreased requirements for exogenous insulin therapy.

HYPOPHYSECTOMY

Microsurgical transsphenoidal hypophysectomy has been reported to be an effective method of treatment for cats with pituitary-dependent hyperadrenocorticism.³⁰ However, because this procedure requires an experienced, highly skilled veterinary surgeon and advanced CT imaging facilities, it remains a highly specialized form of treatment.

Hypophysectomy appears to be highly effective, at least in cats with a small pituitary tumor, but is associated with significant morbidity, and the procedure is not likely to be effective in cats with a large

*References 14, 15, 17, 21, 33, 41, 54.

pituitary adenoma. Another disadvantage of this treatment is that hypopituitarism develops during the immediate postoperative period, resulting in hypocortisolism, hypothyroidism, and transient diabetes insipidus (DI); therefore substitution therapy with glucocorticoids, thyroxine, and desmopressin are required for at least 2 to 4 weeks or lifelong after hypophysectomy.

Prognosis

Hyperadrenocorticism is a serious disease with a guarded to grave prognosis. Without treatment most cats will succumb to complications of the disease within a few weeks to months of diagnosis.^{14,17,41} One common reason for death of untreated cats is the deleterious effects of glucocorticoid excess on skin fragility, which leads to tearing of skin, open wounds, and delayed wound healing. The immunosuppressive effects of glucocorticoid excess also predispose cats to infection. Finally, chronic hypercortisolism can affect the cardiovascular system, resulting in hypertension, pulmonary thromboembolism, or congestive heart failure.

CATECHOLAMINE-SECRETING ADRENAL TUMORS

Pheochromocytoma is a catecholamine-producing tumor derived from the chromaffin cells of the adrenal medulla that is extremely rare in cats.^{2,41} Clinical signs and physical examination findings develop as a result of the space-occupying nature of the tumor and its metastases or as a result of excessive secretion of catecholamines and their impact on blood pressure and cardiac function. A diagnosis of pheochromocytoma before surgery is usually one of exclusion. Unlike a cortisol-secreting adrenal tumor, the contralateral adrenal gland should be normal in size and shape with a catecholamine-producing adrenal tumor. Catecholamine secretion by the tumor, and thus systemic hypertension, tends to be episodic; failure to document systemic hypertension does not rule out pheochromocytoma. Measurement of urinary catecholamine concentrations or their metabolites can strengthen the tentative diagnosis of pheochromocytoma but is not commonly performed in cats. Preliminary studies indicate that plasma normetanephrine levels may be a potential diagnostic test for pheochromocytoma in cats.⁵⁵ Because many of the clinical signs and blood pressure alterations are similar for pheochromocytoma and adrenal-dependent hyperadrenocorticism, it is important to rule out adrenal-dependent hyperadrenocorticism before focusing on pheochromocytoma.

SEX HORMONE-SECRETING ADRENAL TUMORS

A functional tumor arising from the adrenal cortex could secrete excessive amounts of adrenal progestagens, androgens, or estrogens. Progesterone-secreting adrenal tumors have been the most common sex hormone secreting adrenal tumor reported in cats.* Clinical signs are similar to those in cats with cortisol-secreting tumors. Excessive progesterone secretion in affected cats causes DM and fragile skin syndrome, which is characterized by progressively worsening dermal and epidermal atrophy, endocrine alopecia, and easily torn skin.

Recently, a male cat that had developed a strong urine odor and aggressive behavior was documented to have a functional adrenal adenoma associated with high circulating concentration of androstenedione and testosterone.³² After adrenalectomy serum concentrations of the androgens decreased and urine spraying and aggression resolved.

Some adrenocortical tumors, especially carcinomas, may secrete glucocorticoids or sex steroids in addition to mineralocorticoids. In particular, hyperprogesteronism with associated DM has been reported in combination with hyperaldosteronism in two cats.^{9,12} The putative mechanism for concurrent hyperprogesteronism and hyperaldosteronism is either increased production of progesterone, as an intermediate in the synthesis of aldosterone, from neoplastic cells of the zona glomerulosa alone, or increased secretion of aldosterone and progesterone from neoplastic cells of the zona glomerulosa and fasciculata/reticularis, respectively.

In most cats with sex steroid-secreting adrenal tumors, results of tests of the pituitary-adrenocortical axis are normal to suppressed, and the contralateral adrenal gland is normal in size and shape on abdominal ultrasound. Diagnosis requires documenting an increased concentration of one or more adrenal sex steroids, ideally measured before and after ACTH stimulation.

HYPERALDOSTERONISM

Etiology and Pathophysiology

Aldosterone is the major mineralocorticoid secreted by the adrenal cortex and, as such, is responsible for regulation of the body's sodium and potassium balance, as well as maintenance of intravascular fluid volume and acid-base status. Hyperaldosteronism, a condition resulting from increased secretion of aldosterone from the adrenal glomerulosa, may be related to either a primary or a secondary cause.

*References 6, 7, 9, 12, 42, 47.

Secondary hyperaldosteronism develops in cats, as in other species, as a physiologic response to stimulation of the renin–angiotensin–aldosterone system. The renin–angiotensin–aldosterone system acts to maintain the volume of extracellular fluid, circulatory pressure, and electrolyte homeostasis through integrated effects of enzymes and hormones, chiefly on the vasculature and kidney. Therefore secondary hyperaldosteronism can develop in any disease that overstimulates the renin–angiotensin–aldosterone system, such as dehydration, hypotension, or reduced renal perfusion secondary to renal disease.

Primary hyperaldosteronism (Conn's syndrome) appears to be a relatively rare disease of older cats characterized by excessive autonomous secretion of aldosterone from one or both adrenal glands, resulting in clinical signs relating to hypertension or hypokalemia or both.* About one half of cats with primary hyperaldosteronism have unilateral aldosterone-secreting adrenal adenomas, and most of the remaining cats have unilateral adrenal carcinomas. Rarely, cats with Conn's syndrome develop bilateral adrenocortical tumors.⁴² Finally, bilateral adrenal hyperplasia of the zona glomerulosa can also cause primary hyperaldosteronism in cats, but the prevalence of nontumorous disease is unclear.²² Until recently, primary hyperaldosteronism in cats was considered a rare disease, but it is now becoming increasingly recognized as a cause of hypokalemia and hypertension in cats.

Clinical Features

Signalment

Primary hyperaldosteronism is a disease of the middle-aged to older cat. There does not appear to be any breed or sex predilection.⁴⁴

Clinical Signs and Physical Examination Findings

The signs associated with hyperaldosteronism are due to sodium retention (which leads to hypertension) and potassium depletion (which leads to weakness). Historical findings are generally nonspecific and can include generalized weakness (sometimes episodic), lethargy, depression, stiffness, muscle pain, blindness, polyuria, and polydipsia.^t Physical examination findings might include ventroflexion of the neck, hypertension, blindness, and retinal vessel tortuosity or retinal detachment.

The major clinical signs exhibited by the cat depend, in part, on whether primary hyperaldosteronism results from adrenal adenoma, carcinoma, or bilateral adrenocortical hyperplasia. Although the presenting clinical signs relate directly to the increased circulating aldosterone concentrations, they can be divided broadly into

two general subgroups, which include hypokalemic polymyopathy and acute onset of blindness.

HYPOKALEMIC POLYMYOPATHY

Hypokalemic polymyopathy is the most common presentation for cats with primary hyperaldosteronism caused by adrenal adenoma or carcinoma.* These cats develop generalized muscle dysfunction, and owners may report cervical ventroflexion; hind limb weakness; ataxia; and, less commonly, limb stiffness or collapse. In some cats the muscular features are mild and episodic, whereas in others the signs are severe and acute in onset. This presentation is less common in the subgroup of cats with bilateral adrenal hyperplasia, with only about one quarter developing signs related to hypokalemia.²²

ACUTE ONSET OF BLINDNESS

Although subclinical hypertension is common in cats with primary hyperaldosteronism caused by adrenal neoplasia, acute blindness secondary to intraocular hemorrhage or retinal detachment is relatively rare in that subgroup of cats. In contrast, hypertensive retinopathy appears to be the most common presenting sign in cats with primary hyperaldosteronism associated with bilateral adrenal hyperplasia. More than one half of cats with bilateral adrenocortical hyperplasia present with retinal detachment or subretinal, intraretinal, and intravitreal hemorrhages associated with severe systemic hypertension.²²

Routine Laboratory Findings

No specific hematologic abnormalities have been identified in cats with primary hyperaldosteronism. Serum chemistry analysis commonly reveals hypokalemia but its severity is variable. However, because hypokalemia develops in cats for many other reasons, most commonly renal disease, hyperaldosteronism is commonly overlooked as a differential by many veterinarians simply because they do not realize that the condition exists.

Most cats with primary hyperaldosteronism caused by adrenal neoplasia are examined because of clinical signs related to hypokalemia.^t Persistence of hypokalemia despite supplementation with potassium should always prompt suspicion of the possibility of hyperaldosteronism in cats.

Although hypokalemia is common in cats with primary hyperaldosteronism, the finding of a normal potassium concentration in a cat with documented hypertension should never exclude the possibility of primary hyperaldosteronism. In fact, in the reported cats with bilateral adrenal hyperplasia, only one half were mildly hypokalemic at initial presentation, but most had

*References 1, 9, 12, 16, 22, 42, 44-46.

^tReferences 1, 9, 12, 16, 22, 42, 44-46.

*References 1, 9, 12, 16, 42, 44-46.

^tReferences 1, 9, 12, 16, 42, 44-46.

severe hypertension.²² The diagnosis of hyperaldosteronism in such cats would be missed if hypokalemia were considered to be a prerequisite before initiation of a diagnostic evaluation for hyperaldosteronism.

Despite the common finding of hypokalemia, serum sodium concentrations usually are normal. Hypernatremia, when present, is generally mild. The lack of marked hypernatremia in cats with primary hyperaldosteronism may be explained by concurrent volume expansion secondary to sodium retention.

High creatine kinase activity is common in cats with hypokalemic myopathy, but the degree of enzyme elevation is highly variable. A metabolic alkalosis may be observed, which is related to aldosterone-mediated urinary excretion of hydrogen ions. Serum urea nitrogen and creatinine may be slightly high at the time of diagnosis, and progression of renal disease may be the cause of death in some cats with primary hyperaldosteronism. The presence of azotemia may hinder the diagnosis in some cases because the presence of hypokalemia or hypertension may simply be considered a consequence of the renal disease itself.

In human beings progressive renal disease is a recognized sequela to Conn's syndrome, with renal damage occurring because of a combination of intraglomerular hypertension, inflammation, and renal fibrosis. This is also thought to occur in cats suffering from primary hyperaldosteronism as a result of bilateral adrenal hyperplasia, in which a progressively worsening azotemia is a common finding.²²

Diagnostic Imaging

Adrenal masses are rarely visible radiographically. However, if an adrenal mass is seen on radiographs, it is more likely to be an adrenocortical carcinoma than an adenoma. Bilateral adrenocortical hyperplasia, of course, would never be detected on radiographic examination.

In most cats with primary hyperaldosteronism caused by adrenal neoplasia, abdominal ultrasonography is a valuable aid for confirming the presence of an adrenal mass (Figure 24-26). In these cats the contralateral adrenal gland should appear normal in size and shape. It is important that the contralateral gland be assessed to help differentiate a unilateral adrenal tumor from bilateral adrenal hyperplasia. Ultrasonography also should attempt to identify the presence and degree of invasion of the caudal vena cava by the tumor or related thrombus and the presence of metastases to other organs, such as the liver.

Diagnosis

Plasma Aldosterone Concentration

The possibility of primary hyperaldosteronism should be considered in any cat with a history of hypokalemia

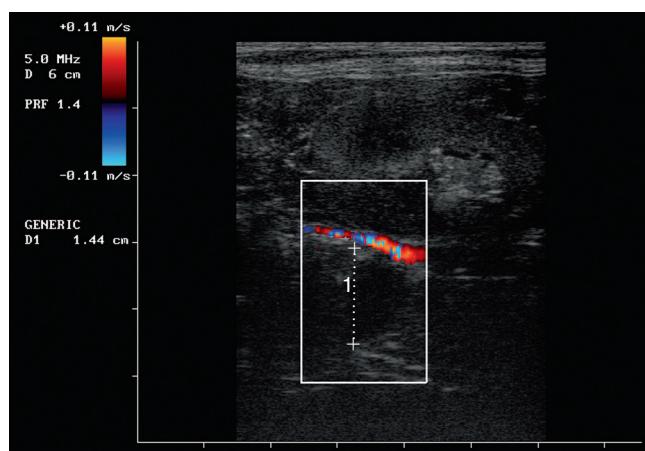


FIGURE 24-26 Ultrasonographic appearance of adrenal gland in a cat with hyperaldosteronism showing proximity of vasculature (shown with color Doppler). Hemorrhage is the major surgical risk associated with adrenalectomy, and ultrasonography can aid in assessing this risk.

or hypertension. Similarly, the finding of an "incidental" adrenal mass by ultrasound should prompt the veterinarian to rule out a functional aldosterone-secreting adrenal tumor.

Confirmation of diagnosis relies mainly on demonstrating a high plasma aldosterone concentration. The assay is widely available at most commercial endocrine laboratories, and requirements for collection and handling of serum or plasma are routine. There is no diagnostic benefit in measuring an ACTH-stimulated aldosterone value over a baseline concentration alone.

Most cats with primary hyperaldosteronism due to adrenal neoplasia have marked elevated circulating aldosterone concentrations.* However, in mild cases of primary hyperaldosteronism, and particularly in cats with bilateral adrenal hyperplasia, it is possible for plasma aldosterone values to be within the upper end of reference range.²² Finally, there may be wide variation in circulating aldosterone concentrations in cats with secondary hyperaldosteronism, with some also developing very high values, so the results must always be assessed together with the clinical signs and laboratory findings.

Ideally, plasma aldosterone concentrations would be interpreted together with plasma renin activity (discussed later). Plasma renin would be expected to be high in cases of secondary hyperaldosteronism and suppressed in cats with primary hyperaldosteronism. However, there are difficulties in measuring plasma renin activity, and it is usually not possible to do so in a clinical situation.

As a consequence, the finding of an adrenal mass together with a markedly high plasma aldosterone concentration is considered sufficient to make a diagnosis

*References 1, 9, 12, 16, 42, 44-46.

of aldosterone-secreting adrenocortical tumor in cats. This is especially true if the cat has persistent hypokalemia or hypertension, or both. Normalization of the high circulating aldosterone concentrations after medical or surgical treatment helps confirm the diagnosis, as does histopathologic confirmation of adrenal neoplasia.

Primary hyperaldosteronism associated with bilateral adrenal hyperplasia is more difficult to diagnose without assessment of plasma renin activity. In these cats potential causes of secondary hyperaldosteronism must always be excluded with appropriate investigations, including evaluation for renal, liver, and cardiac disease. The fact that both cats with primary renal disease and cats with hyperaldosteronism associated with bilateral adrenal hyperplasia develop progressive azotemia is problematic. Without concurrent determination of both plasma aldosterone and plasma renin activity, it is difficult to differentiate these two groups of cats.

Plasma Renin Activity and the Aldosterone–Renin Ratio

Reliably distinguishing primary from secondary hyperaldosteronism requires assessment of activity of the entire renin–angiotensin system by measurement of plasma renin activity (PRA). This can be problematic, insofar as the plasma renin assay is not generally commercially available, and plasma samples must be processed quickly and kept frozen until assayed for renin activity. Furthermore, drugs (e.g., angiotensin-converting enzyme [ACE] inhibitors and beta blockers) and dietary salt intake also may influence PRA measurement.

PRA determinations in cats with primary hyperaldosteronism caused by adrenal neoplasia are usually low to undetectable but may be within the lower half of the reference range in some cats.⁴⁴ Therefore PRA alone cannot be used to diagnose primary hyperaldosteronism, inasmuch as a normal PRA value may be found in cats with primary hyperaldosteronism caused by either an adrenal tumor or bilateral adrenal hyperplasia.^{22,44}

The ratio of plasma aldosterone concentration to PRA, known as the aldosterone–renin ratio, is regarded as the most reliable screening test, with a high aldosterone–renin ratio indicating primary hyperaldosteronism in cats. Even if the plasma aldosterone concentration is within reference range limits, a high aldosterone–renin ratio provides evidence for inappropriate (excessive) aldosterone secretion, diagnostic for primary hyperaldosteronism.²² Cats with secondary hyperaldosteronism, in contrast, have a low aldosterone–renin ratio inasmuch as these cats would be expected to have high PRA values.

Mineralocorticoid Function Tests

In human medicine mineralocorticoid suppression tests are used as confirmatory tests for primary hyperaldosteronism. These suppression tests assess the response to treatments designed to suppress the renin–angiotensin

system and thus decrease circulating concentrations of aldosterone. Examples of mineralocorticoid suppression tests include oral sodium loading, saline infusion, fludrocortisone administration with sodium supplementation, and the captopril challenge test.

Mineralocorticoid suppression tests have recently been developed and are being investigated for use in cats. A recent report assessed changes of the urinary aldosterone-to-creatinine ratio in normal cats in response to increased dietary salt or administration of fludrocortisone acetate.¹³ In that study normal cats showed a more consistent decrease in the urinary aldosterone-to-creatinine ratio with administration of fludrocortisone acetate than with dietary salt supplementation. One cat with an aldosterone-secreting adrenal carcinoma had a high urinary aldosterone-to-creatinine ratio that did not decrease in response to fludrocortisone acetate administration.

Treatment

Initial treatment of primary hyperaldosteronism is directed at controlling hypokalemia, hypertension, or both. Medical treatment of hypokalemia includes parenteral or oral potassium supplementation, as well as correction of any fluid deficits and acid–base imbalances. For this purpose potassium gluconate is generally given at the dosage of 2 to 6 mEq per day, with the dose adjusted as necessary to maintain normokalemia.*

In cats with hypertension, amlodipine besylate (0.625 to 1.25 mg/cat daily) is the initial treatment of choice. Most hypertensive cats become normotensive with amlodipine treatment, but higher doses may be required and hypertension can become refractory to treatment.

If necessary, the diuretic spironolactone, which acts as an aldosterone receptor antagonist, can also be administered at the dosage of 2 to 4 mg/kg/day, assisting in the control of both hypokalemia and hypertension.[†]

Surgical adrenalectomy is the treatment of choice in most cats with hyperaldosteronism that do not have evidence of metastatic disease (see Figure 24-25). For cats with documented unilateral adrenal tumors, surgical adrenalectomy is recommended because it is potentially curative. However, the procedure has been associated with high mortality, with about one third of reported cases dying in the intraoperative or postoperative period as a result of severe acute hemorrhage. Because hyperaldosteronism does not suppress pituitary ACTH secretion, postoperative cortisol insufficiency after excision of unilateral aldosterone-secreting tumors in cats would not be expected to develop. However, it is possible that short-term mineralocorticoid replacement might be needed, especially if postoperative hyperkalemia develops.

*References 1, 9, 12, 16, 42, 44–46.

†References 1, 9, 12, 16, 22, 42, 44–46

Patients should be stabilized medically before surgery, and meticulous preoperative planning is required.⁴⁶ For those cats that have bilateral adrenal hyperplasia or metastatic disease or cats whose owners have declined surgery, medical management with oral spironolactone and potassium can be continued indefinitely.

HYPOADRENOCORTICISM

In cats, as in other species, hypoadrenocorticism results from deficient adrenocortical secretion of glucocorticoids, either alone or concurrent with reduced secretion of mineralocorticoids. Hypoadrenocorticism can be a naturally occurring disease or iatrogenic and is extremely rare in cats (especially the naturally occurring disorder). The first cat with primary hypoadrenocorticism was described approximately 30 years ago,²³ and since then fewer than 20 well-documented cases of naturally occurring adrenal insufficiency in cats have been reported.

Etiology and Pathophysiology

Primary hypoadrenocorticism results from primary adrenal failure, in which destruction of more than 85% to 90% of both adrenal cortices leads to deficient secretion of glucocorticoids and mineralocorticoids.

Secondary hypoadrenocorticism may result from deficient pituitary ACTH secretion, which leads to atrophy of the adrenal cortex and impaired glucocorticoid secretion. In cats with secondary hypoadrenocorticism, the zona glomerulosa is spared, so adequate mineralocorticoid secretion is maintained.

Primary Hypoadrenocorticism

The cause of the complete destruction or atrophy of both adrenal cortices in cats with naturally occurring primary hypoadrenocorticism is usually unknown (idiopathic atrophy). It is likely that many of these cats have immune-mediated destruction of the adrenal cortices, as in humans and dogs with this disease.^{23,37} There are occasional reports of cats with primary hypoadrenocorticism thought to be subsequent to abdominal trauma and adrenal hemorrhage.^{5,8} Primary hypoadrenocorticism has also been described secondary to bilateral adrenal gland infiltration by multicentric lymphoma in two cats.³⁵

Iatrogenic primary hypoadrenocorticism is a rarely reported but well recognized complication of surgical treatment for pituitary-dependent hyperadrenocorticism (Cushing's disease) by bilateral adrenalectomy.¹⁵

Clinical signs in all cats with primary hypoadrenocorticism result from the deficiency of both glucocorticoids and mineralocorticoids. Because the primary insult is to the adrenal glands, pituitary production of ACTH continues unhindered. In fact, reduced cortisol

production results in decreased negative feedback at the pituitary gland, allowing increased release of ACTH. Therefore cats with primary hypoadrenocorticism usually have greatly increased circulating concentrations of ACTH.^{5,37,52}

Secondary Hypoadrenocorticism

Secondary hypoadrenocorticism arises from either (1) an underlying hypothalamic pituitary disorder (such as a pituitary or hypothalamic tumor) resulting in deficient ACTH production or (2) administration of drugs that suppress pituitary ACTH production.^{14,31,41} Secondary hypoadrenocorticism has not yet been recognized as a naturally occurring disorder in cats but is likely to develop in some cats with large pituitary tumors.

Iatrogenic hypoadrenocorticism caused by chronic administration of either glucocorticoids or progestagens is the most common type of secondary adrenocortical failure encountered in cats.^{14,31,36,41} Although hypophysectomy is an uncommon procedure to treat pituitary-dependent hyperadrenocorticism in cats, iatrogenic secondary hypoadrenocorticism is well recognized as a complication of this procedure.²⁸

Deficient ACTH secretion results in a decrease in glucocorticoid production caused by atrophy of the zona fasciculata and zona reticularis. The adrenal zona glomerulosa is preserved because ACTH has little stimulatory effect on mineralocorticoid production. The clinical signs are due to deficiency in glucocorticoid production and so are similar to those observed in cats with primary hypoadrenocorticism. However, the derangements associated with mineralocorticoid deficiency (and subsequent electrolyte disturbances) are absent. Consequently, clinical signs observed are usually less severe than those that develop in cats with primary hypoadrenocorticism.

Clinical Features

Naturally occurring primary hypoadrenocorticism has been well documented in 18 cats.* Of these 18 cats, 14 had idiopathic atrophy of the adrenal cortex, two had traumatically induced hypoadrenocorticism, and two had adrenal lymphoma. The cats documented with idiopathic hypoadrenocorticism were of mixed breed, ranging in age from 1 to 14 years (median age, 4 years), and had no obvious sex predilection.

These 18 reported cats with primary hypoadrenocorticism had clinical signs and physical examination findings similar to those recognized in dogs with the disease. Lethargy, anorexia, and weight loss are the most common presenting signs (Table 24-11). Vomiting, polyuria, and polydipsia are less commonly reported. The clinical manifestations may wax and wane in some cases; this

*References 3, 5, 8, 23, 35, 37, 43, 52, 53.

TABLE 24-11 Clinical Features in 18 Cats with Primary Hypoadrenocorticism

Clinical Features	Number of Cats	% of Cats
HISTORICAL OWNER COMPLAINTS		
Lethargy or depression	18	100%
Anorexia	17	94%
Weight loss	14	78%
Vomiting	10	56%
Waxing and waning course	7	39%
Previous response to therapy	6	33%
Polyuria and polydipsia	5	28%
Dysphagia	1	6%
PHYSICAL EXAMINATION FINDINGS		
Depression	18	100%
Dehydration	16	89%
Weakness	14	78%
Hypothermia	12	67%
Slow capillary refill time	8	44%
Weak pulse	7	39%
Collapse/inability to rise	5	28%
Bradycardia	2	11%
Painful abdomen	1	6%
Constipation	1	6%

temporary remission usually occurs after parenteral fluid and corticosteroid administration.

The most common findings on physical examination are depression, dehydration, weakness, hypothermia, slow capillary refill time, and weak pulse. Collapse, bradycardia, and a painful abdomen are observed less frequently.

Diagnosis

Routine Clinicopathologic Features

HEMATOLOGY

The most noteworthy hematologic findings (if present) in cats with primary hypoadrenocorticism are eosinophilia or lymphocytosis; a mild normocytic, normochromic, nonregenerative anemia is also possible (Table 24-12). The finding of normal or high eosinophil and lymphocyte counts in a sick cat with signs suggestive of hypoadrenocorticism is clinically significant because the expected response to stress is eosinopenia and lymphopenia.

BIOCHEMISTRY

Hyponatremia, hypochloremia, and hyperkalemia are classical electrolyte changes associated with mineralocorticoid deficiency that occur in most cats with primary

TABLE 24-12 Diagnostic Features in 18 Cats with Primary Hypoadrenocorticism

Diagnostic Features	Number of Cats	% of Cats
HEMATOLOGY		
Anemia	5	28%
Lymphocytosis	4	22%
Eosinophilia	1	6%
BIOCHEMISTRY		
Sodium-to-potassium ratio less than 27:1	18	100%
Hyponatremia	18	100%
Hyperkalemia	17	94%
Azotemia	15	83%
Hyperphosphatemia	13	72%
Hypochloremia	13	72%
Low total CO ₂ (metabolic acidosis)	4	22%
Hypercalcemia	3	17%
URINALYSIS		
Specific gravity less than 1.030	10/15	75%
Specific gravity greater than 1.030	5/15	25%
PITUITARY ADRENAL FUNCTION TESTS		
Low basal serum cortisol	17	94%
Subnormal ACTH-stimulated cortisol	17/17	100%
High endogenous ACTH concentration	10/10	100%

ACTH, Adrenocorticotropic hormone.

hypoadrenocorticism (see Table 24-12). Prerenal azotemia and hyperphosphatemia often result from extracellular fluid volume contraction (and subsequent decreased renal perfusion) associated with primary adrenocortical insufficiency (see Table 24-12).

However, most sick cats with altered serum electrolyte changes found on biochemical testing will *not* have primary hypoadrenocorticism. In one study of 49 sick cats with decreased sodium-to-potassium ratios, the final diagnoses included gastrointestinal disease, urinary disease, cardiorespiratory disease, and artefactually decreased Na:K ratios.⁴ None of these 49 cats had a final diagnosis of hypoadrenocorticism.

URINALYSIS

Pretreatment USG varies, but urine may be more dilute than would be expected in a cat with prerenal azotemia. Care must be taken not to misdiagnose primary renal failure in these cases (see Table 24-12). The cause of this apparent loss of renal concentrating ability is poorly understood but may be secondary to renal sodium loss resulting in medullary washout.

Radiography and Electrocardiography

Radiography demonstrated hypoperfusion of the lungs and microcardia in approximately one half of the cats described with primary hypoadrenocorticism.^{3,37,43,52,53}

Electrocardiography revealed sinus bradycardia in 2 of 18 cats, and atrial premature contractions in one.³⁷

Interestingly, no cats with primary hypoadrenocorticism showed the other electrocardiographic changes commonly associated with hyperkalemia in dogs and humans, such as peaking of the T wave, reduced or absent P wave, or atrial standstill.

Pituitary Adrenal Function Tests

ADRENOCORTICOTROPIC HORMONE RESPONSE TEST

The ACTH response test is the most accurate screening test for hypoadrenocorticism in cats. Low basal serum cortisol concentration with a subnormal or negligible response to ACTH is diagnostic for adrenocortical insufficiency but does not differentiate between primary and secondary causes of hypoadrenocorticism. It is imperative to compare test results to reference interval values obtained in healthy cats because cats tend to respond to ACTH with a smaller rise in peak serum cortisol concentrations than dogs.^{14,40}

One common protocol for ACTH response testing in cats is to collect blood for determination of circulating cortisol concentration before and 60 minutes after intravenous administration of 0.125 mg synthetic ACTH (tetracosactide or cosyntropin).^{38,40} It is important to administer ACTH intravenously, especially if the cat is dehydrated. In addition, findings in healthy cats indicate that ACTH given by the intravenous route induces a greater and more prolonged adrenocortical stimulation than does intramuscular administration.³⁸

Many glucocorticoid preparations, including hydrocortisone and prednisolone or prednisone, cross-react in most cortisol assays to give a falsely elevated endogenous cortisol determination and therefore should not be administered until the ACTH response test is completed. Dexamethasone, on the other hand, can be administered before the ACTH response test because it has little or no influence on the measurement of endogenous cortisol concentrations.

A subnormal serum cortisol response to ACTH administration accompanied by serum electrolyte findings of hyperkalemia and hyponatremia is consistent with primary hypoadrenocorticism. If serum electrolytes changes are not found, one of the following may be present:

- Early primary hypoadrenocorticism with at least some residual mineralocorticoid secretion
- Secondary hypoadrenocorticism resulting from pituitary or hypothalamic disease

- Most commonly, secondary hypoadrenocorticism resulting from the administration of drugs such as glucocorticoids or progestagens^{14,31,36,41}

ENDOGENOUS ADRENOCORTICOTROPIC HORMONE CONCENTRATION

Steroid or progestagen administration (or any other iatrogenic cause of hypoadrenocorticism) should first be excluded; then circulating ACTH concentration should be determined to help distinguish between primary and secondary hypoadrenocorticism. Extremely high plasma ACTH concentrations are found in cats with primary hypoadrenocorticism,^{5,37,52} whereas cats with secondary hypoadrenocorticism have inappropriately low plasma ACTH concentrations when compared with circulating cortisol concentrations.^{14,41} Samples for plasma ACTH determination must be collected before treatment with glucocorticoids because these drugs will suppress pituitary ACTH secretion and may therefore result in false normal or low plasma ACTH concentrations in cats with primary hypoadrenocorticism. Special handling is required for blood samples intended for determination of endogenous ACTH concentration because ACTH can degrade rapidly after collection. Mishandling of samples potentially results in falsely decreased values, which could erroneously suggest secondary rather than primary hypoadrenocorticism. Ideally, the veterinarian should speak to laboratory personnel before sampling to be sure to meet the laboratory's requirements.

Treatment

Initial Treatment

In cats with acute or life-threatening primary adrenal failure, initial therapy should be aimed at (1) restoring the circulating blood volume; (2) providing an immediate source of glucocorticoid; and (3) correcting serum electrolyte disturbances (i.e., hyperkalemia, hyponatremia).

FLUID THERAPY

An indwelling intravenous catheter should be placed, preferably in the jugular vein, to allow for the administration of large volumes of isotonic fluids. 0.9% saline is the intravenous fluid of choice and should be administered at 40 to 60 mL/kg per hour during the first 1 to 3 hours. The rate of administration may be slowed before the total bolus has been given if the cat begins to improve. The end point of resuscitation is an improvement in tissue perfusion, clinically recognized by an improvement in mucous membrane color, better-quality pulses, a decrease in the heart rate toward normal, and improved mentation.

Once fluid deficits are restored, the rate of fluid administration should be decreased to maintenance rates of 2.5 mL/kg per hour (60 mL/kg per day), given by constant-rate infusion. Fluid administration is further

tapered when azotemia resolves, serum electrolyte abnormalities are corrected, and the cat is eating and drinking on its own.

GLUCOCORTICOID THERAPY

Rapid intravenous administration of a glucocorticoid is also extremely important in the initial management of severe adrenocortical insufficiency. Dexamethasone, administered at a dose of 0.5 mg/kg intravenously, is adequate in most cases and will not interfere with concurrent ACTH response testing. Hydrocortisone can be administered (as an alternative) at a dose of 5 to 10 mg/kg intravenously every 6 hours or by constant-rate infusion (0.5 to 0.625 mg/kg per hour) for the first 24 hours. These doses are based on studies in dogs because no feline specific dosages have been evaluated. If hydrocortisone is used as initial glucocorticoid therapy, it should not be administered until the ACTH response test has been completed.

Once the ACTH response test has been completed and the cat is stable, glucocorticoid replacement should then be continued as prednisolone at 0.2 mg/kg per day intramuscularly. Transferring to oral administration of the same daily glucocorticoid dosage can be instituted once the cat can swallow without vomiting. In cats use of prednisolone is preferred over the prodrug prednisone, which must be converted to prednisolone to be metabolically active. In one study of cats, only 21% of orally administered prednisone was absorbed and converted to prednisolone in the circulation.¹⁹

MINERALOCORTICOID THERAPY

Mineralocorticoid replacement therapy should also be started once the cat is stabilized and can swallow without vomiting; fludrocortisone acetate is administered orally at 0.1 mg/cat per day.^{14,37,41,43} Desoxycorticosterone pivalate (DOCP) is a mineralocorticoid that also works well in most cats when administered intramuscularly at an initial dosage of 12.5 mg/cat monthly,^{14,37,41,43} although this is not available in most countries other than the United States. The mineralocorticoid effects of either fludrocortisone acetate or DOCP enhance renal potassium excretion and sodium resorption, thereby normalizing serum electrolyte abnormalities.

Signs of weakness, lethargy, and anorexia may persist for 3 to 5 days in cats with acute adrenocortical insufficiency, despite appropriate management. This is in direct contrast to dogs, in which the major clinical signs of primary hypoadrenocorticism usually resolve rapidly within a day or two of treatments.^{37,53}

Long-Term Treatment and Prognosis

Once stabilized, maintenance therapy for cats with primary adrenocortical insufficiency consists of lifelong mineralocorticoid and glucocorticoid supplementation. With appropriate replacement therapy, the long-term

prognosis of cats with primary (especially idiopathic) hypoadrenocorticism is excellent.

Chronic mineralocorticoid therapy can be either fludrocortisone acetate given orally or injections of DOCP given intramuscularly.* The dosage is adjusted as needed, on the basis of serial serum electrolyte concentrations determined every 1 to 2 weeks during the initial maintenance period. The treatment goal with mineralocorticoid supplementation is normalization of the serum sodium and potassium concentrations.

Glucocorticoid replacement, as needed, is usually accomplished with oral administration of prednisolone, at a total dosage of 1 to 1.25 mg daily. If owners find it difficult to administer oral medication, repositol methylprednisolone acetate can be given intramuscularly, at a total dosage of 10 mg monthly. Adverse effects associated with iatrogenic hyperadrenocorticism (i.e., polyuria, polydipsia, polyphagia, pendulous abdomen, hair loss) rarely, if ever, develop in cats at these low replacement glucocorticoid doses.

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PITUITARY DISORDERS

Mark E. Peterson

Disorders of the pituitary gland are rare in the cat. The pituitary disorders that are reported to occur in cats are primarily related to neoplasia (almost exclusively adenomas) of the pars distalis or pars intermedia.^{17,33,70,102} Only one case of a pituitary tumor arising from the pars nervosa (pituitaryoma) has been reported.¹⁰¹ Many pituitary tumors appear to be nonfunctional and are incidental findings at necropsy.^{17,70} Occasionally, clinical signs related to central nervous system dysfunction and

hypopituitarism are observed because of the compressive nature of a large pituitary tumor.^{32,91,101,102} With functional pituitary tumors, clinical disorders that have been reported are limited to those diseases related to increased production of ACTH or GH (i.e., Cushing's disease and acromegaly).^{6,66,67,74,76}

DI, most commonly caused by deficient vasopressin (ADH) secretion from the pars nervosa, is a rare disorder in the cat, with fewer than 20 cases reported.*

ANATOMY AND PHYSIOLOGY

The feline pituitary gland (hypophysis) is a small, whitish, ovoid body (weighing approximately 35 mg in the adult) that lies at the base of the brain in the sella turcica, a concavity of the sphenoid bone.^{25,44,87} Unfortunately, a most confusing terminology has arisen in connection with this gland. The pituitary gland is of dual epithelial and neural origin, with the adenohypophysis (which originates embryologically from an invagination of the buccal cavity) consisting of the pars distalis, pars tuberalis, and pars intermedia and the neurohypophysis (pars nervosa) originating as a direct ventral extension of the diencephalon.^{12,20,25} The pituitary can be divided grossly into two parts, usually referred to as the *anterior* and *posterior lobes*, which are separated by the hypophyseal cleft. On this basis the anterior lobe consists of the pars distalis, whereas the posterior lobe would consist of the pars nervosa and the small strip of cells lying between the pars nervosa and the hypophyseal cleft, the pars intermedia. However, the terms *anterior* and *posterior*, based on the anatomy of the human pituitary, are not totally applicable for the cat, because the feline pars distalis almost completely surrounds the pars nervosa (unlike in humans) and the feline pars nervosa actually lies dorsal, as well as posterior, to the pars distalis.^{12,20,25}

Of all the endocrine glands, the pituitary, affectionately referred to as the *master gland*, is probably the most complex, with many different cell types involved in the secretion and control of a wide variety of trophic hormones. The hormones secreted by the pars distalis include TSH; ACTH or corticotrophin and related hormones (e.g., lipotropins, endorphins); GH; and the gonadotrophic hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH).^{20,76} The pars intermedia is also involved in the secretion of ACTH, endorphins, and melanocyte-stimulating hormones (e.g., alpha-MSH).^{20,73,75,76}

The pars nervosa is probably best noted for its function as a storage depot for arginine vasopressin (AVP, also called *ADH*) and oxytocin. Both vasopressin and oxytocin are produced in cell bodies of the supraoptic, paraventricular, and several accessory nuclei of the hypothalamus. The peptides are then transported along

the axons of the hypothalamo-neurohypophyseal nerve tract and stored in nerve terminals of the pars nervosa in granules until secreted into the circulation.^{20,84}

DISEASES OF THE PITUITARY GLAND

Pituitary Dwarfism

Congenital GH deficiency (pituitary dwarfism), which occurs in dogs secondary to cystic distention of the craniopharyngeal duct, has not been well documented in the cat. Most dwarf cats have either congenital hypothyroidism (see the section on *Thyroid Gland Disorders*) or mucopolysaccharidosis.^{24,35,48,89} One hypothyroid kitten with dwarfism⁸² was found to have low circulating levels of insulin-like growth factor-1 (IGF-1) levels, a peptide hormone produced by the liver after GH stimulation. However, primary GH deficiency has yet to be documented in cats.

Pituitary Macrotumors

Cats with large pituitary tumors may develop signs related to central nervous system dysfunction alone (inactive pituitary tumors) or associated with secretion of the pituitary hormones (Cushing's or acromegaly). Clinical signs that may develop in cats with large invasive pituitary tumors include marked lethargy, weakness, personality change, incoordination, and blindness.^{17,32,91,96}

Because of the large size of these pituitary tumors at the time of diagnosis, surgical removal is generally not feasible.^{51,52,55} Radiation therapy may effectively reduce tumor size and help control neurologic signs in cats with large pituitary tumors.^{50,91}

Adrenocorticotrophic Hormone–Secreting Pituitary Adenomas: Cushing's Disease

As in humans and dogs, hyperfunctioning ACTH-secreting adenomas of the feline pituitary corticotrophs have been reported to cause hyperadrenocorticism (Cushing's disease).* Such tumors may arise from either the pars intermedia or pars distalis corticotroph cells. As in dogs with intermediate lobe adenomas, pars intermedia tumors in the cat can secrete excessive concentrations of endorphins and alpha-MSH, in addition to ACTH.^{73,76} See the section on *Adrenal Gland Disorders*, for more information.

Growth Hormone–Secreting Pituitary Tumors: Acromegaly

In cats, chronic hypersecretion of GH by a functional adenoma of the pituitary gland causes acromegaly, a

*References 4, 14–16, 23, 36, 43, 49, 56, 58, 81, 86, 94, 99.

*References 17, 29, 32, 52, 54, 77, 102.

syndrome characterized by insulin-resistant DM and progressive overgrowth of soft tissue, membranous bone, and viscera.^{30,38,74,76,78}

Published reports of acromegaly in cats are relatively sparse but have been gradually increasing since the disease was first described 30 years ago.* Although thought to be a rare disorder by most veterinarians, recent research suggests that the prevalence underlying acromegaly in cats with diabetes may actually be as high as 25% to 35%.⁶⁶ This strongly suggests that this disorder is greatly underdiagnosed by practicing veterinarians today.⁸⁰

Once secreted by the pituitary, GH exerts its effects on the body through both direct and indirect actions.^{21,57,60} The indirect actions of GH are mediated by IGF-1, a peptide hormone produced by the liver after GH stimulation. IGF-1 has anabolic effects and can induce increased protein synthesis and soft tissue and skeletal growth. By contrast, the direct effects of GH are predominantly catabolic and include lipolysis and restricted cellular glucose transport.

With time, acromegalic cats end up suffering from the catabolic and diabetogenic effects of GH; the anabolic effects of IGF-1; and, in some cases, the space-occupying effect of a pituitary macroadenoma.^{38,67,78} Normally, GH is an important modulator of insulin sensitivity.²⁶ A GH-induced postreceptor defect in insulin action at the level of target tissues leads to concurrent DM, usually associated with severe insulin resistance.^{29,38,67,74,76}

Cause of Acromegaly

In the cat, as in man, acromegaly is most often caused by a GH-secreting adenoma of the pituitary gland.[†] In addition, GH-producing hyperplasia of these cells has also been reported as a rare cause.^{66,67} This latter process might represent a pre-adenomatous change or a separate disease process. Further, one cat with a double pituitary adenoma causing both acromegaly and hyperadrenocorticism has been reported.⁵⁵

As in dogs, administration of progestogens to cats can induce expression of the mammary GH gene and thereby stimulate the local production of GH in mammary tissue.⁵⁹ Indeed, progestin-induced fibroadenomatous changes in the mammary gland of cats are also associated with locally enhanced GH expression. In cats this mammary gene is identical to the pituitary-expressed gene and is driven by the same promoter.⁵⁹ However, this local production of GH has never been shown to result in high circulating GH concentrations or the clinical state of acromegaly in cats.^{67,72}

Clinical Features of Acromegaly

The earliest clinical signs of feline acromegaly, present in almost all cats reported to date, include progressive polyuria, polydipsia, and polyphagia, all of which are associated with poorly controlled or insulin-resistant DM.* Additional clinical findings that may develop in these cats weeks to months after development of diabetes may include enlargement of one or more organs (i.e., heart, liver, kidneys, spleen, tongue), progressive increase in body size and weight, disproportionate enlargement and thickening of the head and paws, prognathia of the lower jaw, degenerative arthropathy, renal failure, congestive heart failure, and central nervous signs caused by enlargement of the pituitary tumor.

The clinical features of feline acromegaly, listed according to the signs that may develop as the disease progresses when left untreated, are presented in Box 24-3. At the time of diagnosis, many diabetic cats with acromegaly do not exhibit the "classic" physical changes associated with the disease, such as enlargement of the face and extremities.^{38,66,67,74} This is one reason that this endocrine disorder has frequently gone undiagnosed or misdiagnosed as "routine" diabetes. It is important to consider acromegaly as a differential diagnosis in all cats with DM, especially if the cat is poorly controlled or develops moderate to severe insulin resistance.

SIGNALMENT

Acromegaly develops in middle-aged to older cats without obvious breed predilection. All reported cases of feline acromegaly have been mixed-breed cats (domestic shorthair). There is a strong male sex predilection, with approximately 90% of cats being male.^{38,66,67,74} This is in contrast to humans, wherein acromegaly has no sex predilection, and in dogs, wherein females are affected most commonly.^{30,78}

GENERAL APPEARANCE

In humans the earliest recognizable signs of acromegaly are soft tissue swelling and hypertrophy of the face and extremities.^{19,57} Overt DM, although it does develop in up to half of human patients with acromegaly, is generally not the initial patient complaint.⁷ Similarly, alterations in facial features and body dimensions are observed in some cats with acromegaly, generally at a later stage of the disease (see Box 24-3). GH-induced proliferation of connective tissue results in an increase in body size, most frequently manifested as marked weight gain and enlargement of the abdomen. The increases in body weight may occur despite the presence of the catabolic state of unregulated DM. As the disease progresses, growth and hypertrophy of all organs in the body (e.g., heart, liver, kidneys, tongue) is also a characteristic sign of acromegaly.

*References 1, 2, 6, 9, 13, 27-29, 34, 37, 46, 47, 53, 55, 61, 68, 74, 85, 93, 95.

[†]References 2, 27, 29, 34, 38, 46, 47, 55, 74.

*References 1, 2, 6, 9, 13, 27-29, 34, 37, 46, 47, 53, 55, 61, 68, 74, 85, 93, 95.

BOX 24-3**Clinical Features of Cats with Untreated Acromegaly: Progression Over Time*****Initial Clinical Signs**

- Polyuria and polydipsia
- Polyphagia
- Diabetes mellitus
- Physical appearance generally quite normal

Clinical Signs Noticed After a Few Weeks

- Insulin resistance (increasing need for high doses of insulin)
- Weight gain/increase in body size
- Abdominal enlargement
- Organomegaly (e.g., liver, kidneys, heart, tongue)

Clinical Signs That May Be Noticed After a Few Months

- Systolic cardiac murmurs
- Respiratory stridor
- Lameness/degenerative arthropathies
- Broad facial features
- Prognathia inferior
- Increase in paw size

Clinical Signs That May Develop After a Few Years

- Renal failure
- Congestive heart failure
- Central nervous system signs

*Not all acromegalic cats will develop all these clinical features.

Cats with acromegaly may also develop mandibular enlargement resulting in prognathism, widened interdental spaces, thickening of the bony ridges of the skull, large head, large paws, and soft tissue swelling of the head and neck (see Box 24-3).^{38,66,67,74} Obviously, not all acromegalic cats will develop all these conformational changes. However, because many of these changes develop and progress gradually, subtle conformational changes might not always be noticeable by owners who see their affected cat every day. Reviewing old photographs of the cat taken years earlier frequently helps determine whether changes in the cat's appearance have indeed occurred (Figure 24-27).

DIABETES MELLITUS

The earliest and most commonly recognized clinical manifestation of acromegaly in most cats is insulin-resistant DM (see Box 24-3). GH, especially in carnivores (and especially in cats and dogs), displays powerful

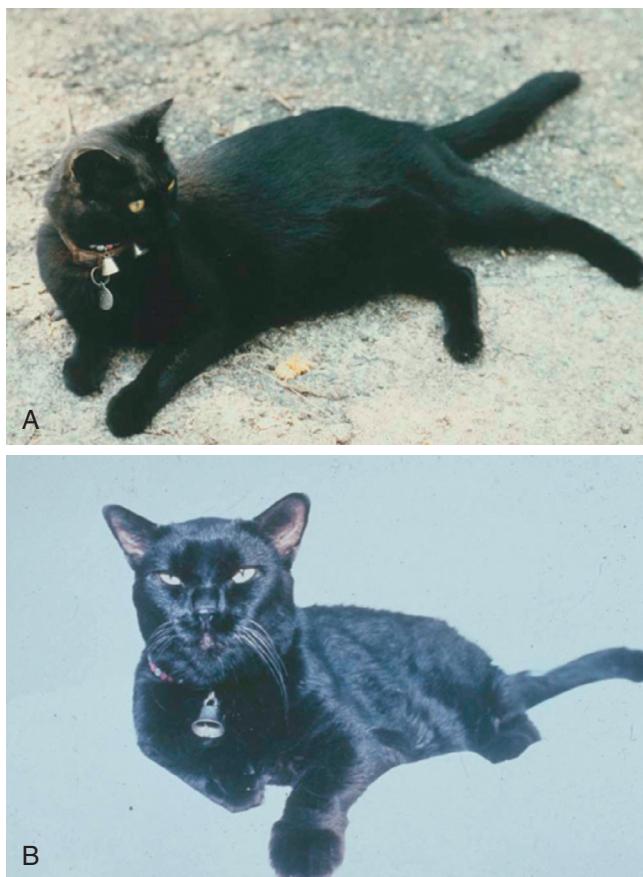


FIGURE 24-27 Photography of a 10-year-old male domestic short-hair before (**A**) and 3 years after (**B**) the diagnosis of insulin-resistant diabetes mellitus. Acromegaly was confirmed 9 months after the onset of the diabetic state. Notice the broad facial features, large head, and club paws development of acromegaly.

diabetogenic activity and appears to provoke hyperglycemia mainly by inducing peripheral insulin resistance.^{8,100} Excessive GH has been shown to decrease insulin receptor numbers, decrease receptor-binding affinity, and induce a postreceptor insulin defect similar to that observed with cortisol-induced insulin antagonism.^{26,62}

Most cats with acromegaly exhibit severe, persistent hyperglycemia that is refractory to insulin therapy and can be controlled only with extremely large doses of exogenous insulin. In one recent study⁶⁶ the mean insulin requirements of 59 acromegalic diabetic cats (14 units daily; range, 2 to 70 units daily) were markedly higher than in a matched group of diabetic cats without acromegaly (6 units daily). Other cats have been reported in which even higher insulin dosages (up to 130 U daily) were needed to control hyperglycemia.⁷⁴ Despite the presence of such uncontrolled DM, the development of ketoacidosis is rare in cats with acromegaly.

Although polyphagia is a well-recognized clinical sign associated with uncontrolled DM, the excess GH itself is also likely to contribute. Some cats with

acromegaly will have persistent, and often extreme, polyphagia, despite reasonable control of the DM.

RESPIRATORY SYSTEM

In cats with acromegaly, GH-induced soft tissue proliferation in the oropharyngeal region can lead to upper airway narrowing, resulting in clinical signs of respiratory disease. In accord with this, inspiratory stridor develops in about half of the cats with acromegaly (see Box 24-3).⁶⁶⁻⁶⁸ Dyspnea may develop in cats with long-standing untreated acromegaly as a result of pulmonary edema or pleural effusion from GH-induced cardiac failure.^{68,74,76}

SKELETAL SYSTEM

In some cats with acromegaly, articular changes (associated with degenerative arthritis) may be severe and crippling (see Box 24-3). The articular changes initially result from fibrous thickening of the joint capsule and related ligaments, as well as bony overgrowth and articular cartilage proliferation.^{10,22} Later, as a result of the distorted joint architecture, features more typical of degenerative joint disease develop. Radiographic evidence of acromegalic arthropathy includes an increase in joint space secondary to thickening of the articular cartilage (early), cortical thickening, osteophyte proliferation, periarticular periosteal reaction, and collapse of the joint.^{10,22,74,76}

Other bony changes that may occur in acromegaly include enlargement of the mandible, leading to prognathism and an overbite by the lower incisors. There also may be increased spacing between the teeth, as commonly occurs in acromegalic dogs.⁷⁸ The bones of the calvarium may be thickened (Figure 24-28), with

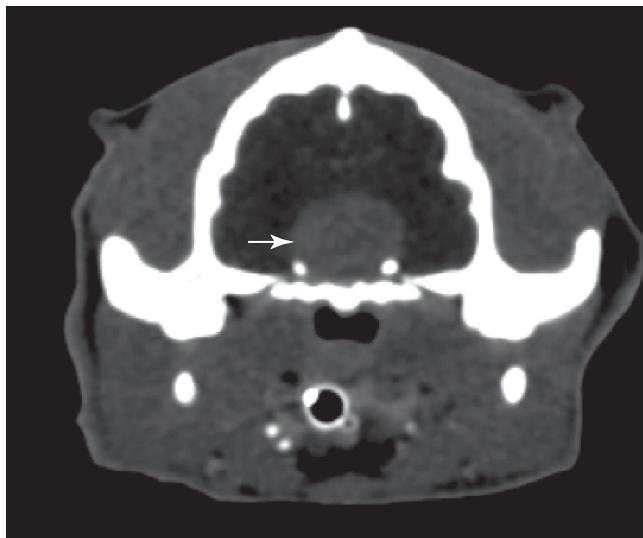


FIGURE 24-28 Computed tomography of the head of a 14-year-old male castrated domestic shorthair with acromegaly. Note the huge pituitary mass, measured at 7.5 mm in height, invading the hypothalamus. Also note the apparent calvarial hyperostosis (thickening of skull).

apparent enlargement of the entire head in some cats. Finally, marked spondylosis deformans of the spine may be evident; this may lead to gait abnormalities such as chronic progressive stiffness and rigidity in some cats.^{66,74}

CARDIOVASCULAR SYSTEM

Another prominent manifestation of chronic acromegaly in some cats is cardiomyopathy. Cardiovascular abnormalities that may be detected on physical examination include the presence of a systolic murmur, gallop rhythm, and, especially late in the course of the disease, signs of congestive heart failure (e.g., dyspnea, muffled heart sounds, ascites) (see Box 24-3). Radiographic findings may include mild to severe cardiomegaly, pleural effusion, and pulmonary edema.^{68,74,76} Echocardiography frequently reveals left ventricular and septal hypertrophy but can also be normal; electrocardiographic findings are generally unremarkable. The cause of cardiac disease in acromegaly is not clear but may be related to the general growth-promoting effect of excess GH on tissues.⁸⁸

Hypertension is common in human patients with acromegaly^{11,98} and may contribute to cardiac hypertrophy in cats.^{38,68} However, in one large case series of acromegalic cats, hypertension was not any more prevalent than would be expected in a group of age-matched control cats.⁶⁶ Nevertheless, blood pressure should be determined in all cats with acromegaly, especially if cardiac disease is present, and that treatment is instituted as needed.

NERVOUS SYSTEM

In cats central nervous system signs can develop as a result of expansion of the pituitary tumor beyond the sella turcica. However, central nervous system signs are uncommon because the GH-secreting pituitary tumors tend to be both benign and slow growing, and overt neurologic signs are rare even when a large pituitary tumor is compressing and invading the hypothalamus (see Figure 24-28).^{66,74,76} When neurologic signs do develop, they may include stupor, somnolence, and poor appetite.

RENAL SYSTEM

Polyuria and polydipsia are common signs of acromegaly in cats and appear to develop primarily because of the associated diabetic state. However, acromegaly also produces several other alterations in renal function. The kidneys may hypertrophy, and GFR and renal plasma flow may increase. The nephromegaly is also associated with an increase in both secretory and absorptive functions.^{5,69} In cats with long-standing acromegaly, however, development of azotemia, proteinuria, and clinical signs of renal failure commonly develop (see Box 24-3). Histologically, the kidneys of acromegalic cats can show mesangial thickening of the glomeruli, changes similar

to those described in human patients with diabetic nephropathy. Although the mechanism of impairment of renal function in feline acromegaly is not clear, it may result from the glomerulosclerosis associated with the unregulated DM or GH-mediated glomerular hyperfiltration.

Diagnosis of Acromegaly

Confirming a diagnosis of acromegaly can be difficult because of the disorder's insidious onset, the cost of pituitary imaging procedures, and the frequent lack of a readily available GH assay validated for use in cats.^{30,38,67,76} As is the case in many feline endocrinopathies, a combination of suggestive clinical features and multiple diagnostic tests is generally required to make the definitive diagnosis of acromegaly (Box 24-4).

Acromegaly should be suspected in any cat that has severe insulin-resistant DM (persistent hyperglycemia despite daily insulin doses greater than 10 U daily), especially if other characteristic signs of acromegaly (especially arthropathy or cardiomyopathy) are also present. The diagnosis of acromegaly can be established by demonstrating markedly elevated circulating GH or IGF-1 concentrations, especially when combined with the finding of a pituitary mass with brain imaging (see Box 24-4).

ROUTINE LABORATORY TESTING

In addition to findings expected in a poorly controlled diabetic cat (e.g., hyperglycemia and glycosuria),

clinicopathologic testing of an acromegalic cat may reveal high serum hepatic enzyme activities, hyperproteinemia, hyperphosphatemia, proteinuria, and mild erythrocytosis.^{38,67,68,74}

Mild increases in the activities of serum ALT and ALP appear to develop secondary to the hepatic lipidosis associated with the GH-induced DM. Mild hyperphosphatemia appeared to be caused by a GH-induced increase in the renal tubular reabsorption of phosphate.^{39,92} The mechanism of the hyperproteinemia (which is associated with a normal pattern of distribution on serum protein electrophoresis) is unclear but is relatively common, occurring in over half of cats.^{66,74} Mild erythrocytosis, which also develops in some cats with acromegaly, probably represents another manifestation of the anabolic effects of excessive GH.

In the latter stages of the disease, routine laboratory tests may reveal high serum concentrations of urea nitrogen and creatinine, as the cat develops renal disease as a complication of the acromegalic state.^{68,74}

SERUM GROWTH HORMONE CONCENTRATION

Ideally, the diagnosis of acromegaly is confirmed by demonstrating high serum GH concentrations, the primary hormone responsible for the disease. Overall, use of basal serum GH concentrations appears to be the most accurate diagnostic test for feline acromegaly. All cats with acromegaly thus far reported have had clearly high GH concentrations.* This is in contrast to the normal serum IGF-1 values occasionally reported in some cats with acromegaly (see the discussion later in this chapter on serum insulin-like growth factor-1 concentration).^{68,85}

In a recent study a validated feline GH radioimmunoassay proved useful in distinguishing 19 clinically normal cats from 19 acromegalic cats, with no overlap occurring between the two groups.⁶⁵ In a separate study using the same feline GH assay, however, 2 out of 34 diabetic cats (without acromegaly) were wrongly classified as being acromegalic using the same diagnostic criteria. Nevertheless, the specificity and sensitivity of this assay were both high at 95% and 84%, respectively.⁶⁶

Although many acromegalic cats have been diagnosed by demonstrating high serum or plasma GH concentrations, this test has never been widely available to the practicing veterinarian; the assay is performed in only a few specialized laboratories around the world. A GH radioimmunoassay validated for both dogs and cats has been available at Utrecht University, The Netherlands, for many years,^{53,93} and a validated feline GH assay is now available at the Royal Veterinary College, University of London.⁶⁵ But even in the best of circumstances, it remains extremely inconvenient for most practicing veterinarians to ship frozen samples to Europe

BOX 24-4

Diagnosis of Acromegaly in Cats

Supportive Clinical Features

Insulin-resistant diabetes mellitus (daily insulin doses of >2 IU/kg)

Changes in physical appearance (larger head or paws)

Weight gain despite poorly controlled diabetes

Routine Laboratory Findings

Hyperglycemia and glucosuria

Lack of ketonuria

Hyperproteinemia

Specific Tests for Acromegaly

High serum or plasma growth hormone concentrations
High serum insulin-like growth factor-1 concentrations

Pituitary Imaging

Pituitary tumor on computed tomography or magnetic resonance imaging

*References 28, 34, 46, 65, 66, 74, 93.

for serum GH analysis. The fact that most veterinarians do not have convenient access to a veterinary laboratory capable of measuring serum GH has greatly hindered the diagnostic evaluation of cats with suspected acromegaly.

Because of this lack of GH assays for cats, the diagnosis of feline acromegaly generally must be based on the characteristic clinical, laboratory, and imaging features (see Boxes 24-3 and 24-4) with demonstration of a high serum IGF-1 concentration alone (discussed in the next section).

SERUM INSULIN-LIKE GROWTH FACTOR-1 CONCENTRATION

In human medicine, determination of circulating concentrations of the polypeptide hormone IGF-1 is a very useful diagnostic test for acromegaly. The basis for use of IGF-1 as a diagnostic test for acromegaly is that circulating GH activates the hepatic and peripheral tissue production of IGF-1, which is responsible for many of the actions normally attributable to GH itself. In fact, other than DM, most of the clinical features of acromegaly are *not* the result of a direct catabolic effect of GH excess, but rather result from an indirect anabolic effect of GH excess mediated through the production of the IGF-1 (e.g., overgrowth of soft tissue, bony enlargement, and organomegaly).⁵⁷ Therefore circulating IGF-1 levels serve as a biomarker for assessing the peripheral biological effect of GH hypersecretion, which, at least in human patients, tends to correlate better with the severity of the acromegalic state than does random circulating GH determinations.

In cats with suspected acromegaly, use of IGF-1 measurements is also a very useful diagnostic test, with many studies now demonstrating that serum IGF-1 can differentiate cats with acromegaly from clinically normal cats.^{2,6,66,68,85} For the practicing veterinarian, IGF-1 determinations are widely available and are performed by most commercial veterinary laboratories, in contrast to the limited availability of feline GH assays.

As with all diagnostic tests, however, the serum IGF-1 test is not a perfect test for acromegaly. An abnormally high serum IGF-1 concentration strongly suggests acromegaly, but the disease should not be excluded if values are within the high-normal range. Portal insulin is necessary for hepatic IGF-1 production, which means that in an acromegalic diabetic cat before or at the start of insulin therapy, IGF-1 can prove falsely low.⁸⁵ However with insulin treatment the IGF-1 level may well eventually increase into the acromegalic range with increasing portal insulin concentrations. In one study the sensitivity of IGF-1 as a diagnostic test for feline acromegaly was calculated to 0.84 (positive diagnostic test in 84% of the acromegalic cats tested);⁶ accordingly, that indicates that 16% of acromegalic cats would be expected to have

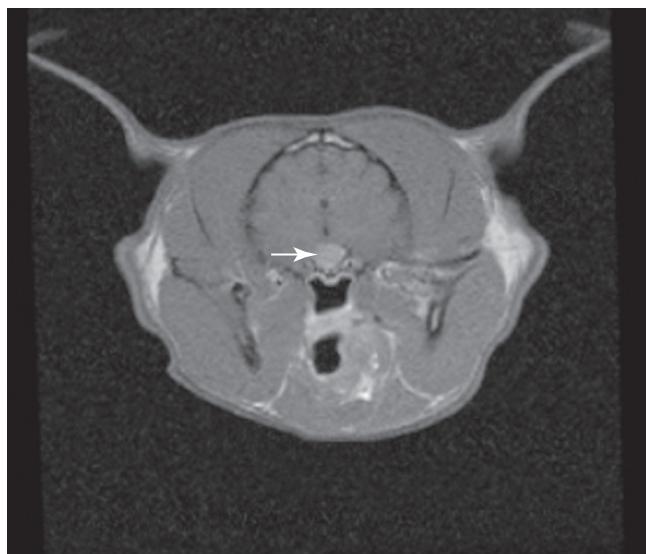


FIGURE 24-29 Magnetic resonance imaging of the brain of a 12-year-old male castrated domestic shorthair with acromegaly. Notice the obvious pituitary mass, measured at 1.9 mm in height.

single IGF-1 values that were within reference range limits (false-negative test result).

In addition, high serum IGF-1 concentrations have recently been reported in diabetic cats *without* acromegaly, so false-positive test results can also occur.^{45,95} In one study the test specificity of IGF-1 in cats without acromegaly was calculated to be 0.92 (normal test result in 92% of the nonacromegalic cats evaluated);⁶ accordingly, that indicates that 8% of cats without acromegaly would be expected to have a false-positive, high IGF-1 value.

PITUITARY IMAGING PROCEDURES

Documentation of a pituitary mass by CT or MRI provides further support for the diagnosis (Figures 24-28 and 24-29). It appears that MRI may be a more sensitive diagnostic test for this condition.²⁹ However, although almost all cats with acromegaly have a clearly visible pituitary tumor on CT or MRI imaging, it should be remembered that normal intracranial imaging (no visible pituitary tumor) does preclude a diagnosis of feline acromegaly.^{66,67}

In addition to documenting the presence of a pituitary tumor, determining the size and location of the tumor is helpful in establishing the mode of therapy (i.e., surgery, medical, radiotherapy) and monitoring the tumor response to therapy.^{27,47,50,55,91}

Differential Diagnoses for Acromegaly

Any disease causing insulin-resistant diabetes should be considered a differential diagnosis for acromegaly, as should diabetes management issues that can lead one to suspect insulin resistance (e.g., lack of compliance,

inappropriate insulin storage, and administration problems).

Hyperadrenocorticism, especially the pituitary-dependent form of the disease, is the major differential for acromegaly for many reasons. First of all, both acromegaly and hyperadrenocorticism commonly cause insulin-resistant DM.^{76,90} Both disorders are caused by a hormone-secreting (ACTH or GH) pituitary tumor, and bilateral adrenal enlargement is common in both acromegaly and pituitary-dependent hyperadrenocorticism.^{66,74}

Differentiating between the two disorders is sometimes difficult. However, looking at specific clinical signs for each disease is generally quite helpful in making the differentiation. For example, broad facial features, clubbed paws, arthropathy, and prognathia inferior should lead the veterinarian to suspect feline acromegaly, whereas truncal hair loss; pendulous abdomen; and thin, fragile, or tearing skin are associated with hyperadrenocorticism (see the section on [Adrenal Gland Disorders](#)). In addition, the insulin resistance associated with acromegaly is usually much more severe than that observed in cats with hyperadrenocorticism, as demonstrated by their much higher insulin requirements. Finally, dexamethasone suppression tests have generally proved useful in differentiating the two disorders because tests of the pituitary–adrenal axis generally remain normal in cats with acromegaly.^{30,76}

Treatment of Acromegaly

In acromegalic cats three potential treatment options are available, including external radiation therapy, hypophysectomy, and medical therapy. Of these, radiotherapy is currently considered to be the most effective, although the response can vary in individual cats.

Conservative supportive treatment also represents a genuine alternative option, especially in cats for which definitive treatment is simply not possible (e.g., too costly). It is possible for an acromegalic cat to maintain a reasonable quality of life if it receives high (and generally increasing) daily doses of insulin to treat the insulin-resistant DM.

EXTERNAL RADIATION THERAPY

Currently, radiotherapy is considered by most to be the best treatment option for cats with acromegaly. Although earlier reports suggested that radiotherapy for cats with acromegaly offered only a limited or partial response, more recent studies indicate that most acromegalic cats respond favorably to external radiation therapy.^{27,34,50,91} In cats that have a good to excellent response to radiotherapy, pituitary tumors generally decrease in size and high circulating concentrations of GH normalize. In such cats insulin resistance resolves and overall diabetic control improves; some cats may even go into diabetic remission.^{27,34}

Despite the fact that external radiation therapy remains the most effective treatment for cats with acromegaly, this treatment modality has many disadvantages. The most important drawbacks to this treatment include the limited availability, the need for frequent hospital visits and multiple anesthetic procedures, and the high cost.^{27,34,50,91} In addition, it is not uncommon for cats to relapse months to years after treatment, with recurrence of uncontrolled or insulin-resistant DM.⁷⁴

The final outcome of radiotherapy is not always predictable. Not all cats will respond completely to radiotherapy, with some showing improvement of DM but persistence of other acromegalic signs. In many of these latter cats, serum GH normalizes but serum IGF-1 concentrations remain high (so-called GH–IGF-1 discordance).^{65,67} This suggests that radiotherapy may decrease circulating GH concentration to levels such that diabetogenic effects are no longer present but not to a level required to normalize IGF-1 secretion and reverse its associated biological complications.^{27,47,67} Because of this GH–IGF-1 discordance, use of serum GH concentrations alone are not recommended as a marker to judge cure of the acromegalic state after treatment.

SURGICAL THERAPY (HYPOPHYSECTOMY)

Hypophysectomy, the therapeutic modality of choice for human patients suffering from acromegaly, may also appear to be a logical choice for cats with GH-secreting tumors. In human patients, however, surgical cure is most likely to result if the pituitary tumor is small and noninvasive. Large, invasive pituitary tumors, similar to those identified in many cats with acromegaly, are only rarely cured by surgery.^{19,57}

Experience with transsphenoidal hypophysectomy as a treatment for cats with acromegaly is very limited. It is a highly specialized procedure and is not likely to be available to many clinicians in the near future. This surgical procedure is also associated with relatively high morbidity and mortality rates.⁵² However, in cats with small pituitary tumors, hypophysectomy can be curative.⁵⁵

Cryohypophysectomy represents an alternative technique that was successful in treatment of two reported cats with acromegaly. However, this technique also requires further evaluation and longer-term follow-up before it can be strongly recommended.^{2,3,9}

MEDICAL THERAPY

Compared with the situation in human patients, only limited information is available on medical treatment of cats with acromegaly. In human patients three types of medication are used in the treatment of acromegaly, all with variable degrees of success.^{18,57}

First-line medical treatment for acromegaly included the use of the somatostatin analogs (e.g., octreotide and lanreotide). These analogs are synthetic forms of the

hypothalamic hormone, somatostatin, which acts to inhibit GH production. These drugs improve symptoms and signs of acromegaly in the majority of human patients, with normalization of the serum GH and IGF-1 concentrations in 50% to 70%.^{18,19,57}

Dopamine agonists (e.g., bromocriptine and selegiline) make up the second medication group. These drugs are not as effective as the other medications at lowering GH or IGF-I levels and also cause more adverse effects.

The third group of drugs for the medical treatment of acromegaly is the use of a GH receptor antagonist (pegvisomant). By blocking the action of the endogenous GH molecules, this compound is able to normalize IGF-I levels and control disease activity in virtually all patients.^{18,19,57} The disadvantage of this form of medical therapy is that the drug is not directed at the pituitary tumor itself but at the peripheral GH receptor sites; therefore the pituitary tumor continues to grow, and the circulating GH concentrations remain high.

Although medical treatment for acromegaly would be a very attractive option for many cat owners, neither somatostatin analogs nor dopamine agonists have been successful in lowering serum GH concentrations or improving insulin sensitivity in cats with acromegaly.^{1,61,74,76} A recent study did show an acute lowering of serum GH after intravenous octreotide administration, suggesting that perhaps a small subset of cats with acromegaly might be suited to treatment with somatostatin analogs.⁹³ However, a recent trial with lanreotide, a long-acting somatostatin analog, produced disappointing results in cats with acromegaly.⁶⁷ It may be that at least some GH-secreting pituitary adenomas of cats lack the somatostatin receptors possessing high affinity for the somatostatin analogs, thereby explaining the apparent lack of effect of these drugs in cats.

Pegvisomant has not yet been evaluated in cats with acromegaly; however, this drug would be expected to be effective only if there is sufficient homology between feline and human GH receptors. In addition, the drug must be given daily by subcutaneous injection and might be too costly for many cat owners.

Prognosis of Acromegaly

In cats with acromegaly, the severity of clinical signs and clinical course are related to the high circulating GH and IGF-1 concentrations, as well as the duration of the disease. The short-term prognosis for most cats with acromegaly is relatively good. Severe insulin-resistant DM can generally be satisfactorily controlled using large, divided doses of insulin. Mild to moderate cardiac disease responds well to diuretic therapy and ACE inhibitors (i.e., enalapril or benazepril), at least initially.

Definitive treatment with external radiation therapy or hypophysectomy improves long-term prognosis, but complete long-term cure of feline acromegaly is rare. Survival times of both aggressively and conservatively

treated cats vary enormously, with some cats not surviving more than a few weeks beyond diagnosis and others living for many years (>5 years) and dying from causes likely unrelated to the disease. If left untreated, most cats eventually die or are euthanized because of the development of severe congestive heart failure, renal failure, respiratory distress, or the neurologic effects of an expanding pituitary tumor.

Diabetes Insipidus

DI is an uncommon condition characterized by marked polyuria and secondary polydipsia. The disorder may be classified as either neurogenic (central) or nephrogenic in origin. Central DI results from a complete or partial failure of the neurohypophysis to secrete vasopressin (also called ADH), whereas nephrogenic DI is related to a lack of renal responsiveness to the antidiuretic actions of vasopressin.^{31,79}

Cause of Diabetes Insipidus in Cats

DI is an extremely rare disorder in cats, with only 18 reported cases.* All cats have had central DI; a primary nephrogenic form of DI (congenital DI) has not yet been described in cats. As in dogs, cats can develop either partial or complete forms of central DI.^{58,86,94}

In most cats the exact cause of the disorder cannot be determined (idiopathic DI) but is thought to be a congenital defect in vasopressin secretion. Head trauma, however, is a relatively common identifiable cause of DI in cats, with about a third of the reported cases having such a history.^{4,16,56,86,94} Other less common causes of DI in cats include pituitary macrotumors³¹ or pituitary malformation.⁹⁹

Clinical Features of Diabetes Insipidus

All 18 reported cats with DI have been kittens or young adults, with an average age at diagnosis of 16 months (range, 2 months to 5 years).† Of the 18 cats, 12 (67%) have been males. There is no breed predilection.

The major clinical signs of feline DI are marked polydipsia (generally above 100 mL/kg daily; normal, 40 to 70 mL/kg daily) and polyuria, usually of several months' duration.⁷⁹ The severity of clinical signs varies because DI may result from a partial to complete defect in either arginine vasopressin secretion or action. Other clinical signs affected cats show less consistently include weight loss (resulting from a preoccupation with drinking) and dehydration (if access to water has been restricted). Physical examination findings are usually unremarkable.

*References 4, 14-16, 23, 36, 43, 49, 56, 58, 81, 86, 94, 99.

†References 4, 14-16, 23, 36, 43, 49, 56, 58, 81, 86, 94, 99.

Diagnostic Workup for Polyuria and Polydipsia

The first step for any cat presented with the owner complaint of polyuria and polydipsia is to establish that the problem actually exists, preferably by a combination of history; random USG determinations; and, if necessary, home measurement of water consumption over several days.

The diagnosis of DI requires that it be differentiated from other medical diseases that cause polyuria and polydipsia in cats.^{64,79} The most important ones to rule out for polyuria and polydipsia in cats include primary renal disease, DM, and hyperthyroidism, all of which are much more common than DI. Although primary (psychogenic) polydipsia, a rare disorder associated with compulsive water drinking, has not been well-documented in the cat, it may play a role in the polyuria and polydipsia that develops in more than a third of cats with hyperthyroidism.^{71,83}

In general, routine hematologic and serum biochemical testing in cats with central DI are either normal or show evidence of mild dehydration (e.g., mild increases in packed cell volume, total protein, and sodium). In contrast, most of the other differential disorders for polyuria and polydipsia result in marked abnormalities in these screening tests (e.g., elevated serum urea nitrogen, creatinine, glucose, or T₄).

In central DI complete urinalysis is unremarkable except for the finding of persistently dilute urine. In cats the finding of USGs consistently below 1.008 is usually associated with either DI or hyperthyroidism.^{71,79} Obviously, hyperthyroidism should be ruled out before initiating testing procedures for DI. It is important to realize that the finding of a USG below 1.008 in a cat excludes mild (occult) renal disease, so further workup for renal disease or precautions associated with the water deprivation test are not necessary.

The workup for polyuric cats with USGs about 1.008 is more complicated. Finding a USG of 1.008 to 1.012 or greater (but less than 1.030) can be associated with hyperthyroidism, stage 1 (occult) renal insufficiency, or pyelonephritis, as well as partial forms of central DI.^{71,79} The first step in workup of this group of cats is to exclude hyperthyroidism.

If the serum T₄ concentration is normal, pyelonephritis and early renal insufficiency should next be ruled out. The veterinarian should never perform a water deprivation test in a cat until renal disease is excluded, inasmuch as water deprivation could induce overt renal failure or urosepsis in a cat with unsuspected renal insufficiency.^{31,79}

For the workup of pyelonephritis and early renal insufficiency, the following stepwise diagnostic approach is recommended. First, the veterinarian should perform a urine culture to help exclude pyelonephritis and associated urinary tract infection. If the urine culture is

negative, renal size and architecture are evaluated by abdominal radiography or, preferably, renal ultrasonography.^{42,79} If urine culture results are negative and radiographic or ultrasonographic findings are equivocal, determination of GFR⁴⁰ or renal biopsy⁹⁷ may be indicated. Because the urine culture can sometimes be negative in cats with pyelonephritis, a therapeutic trial with an appropriate antibiotic (e.g., enrofloxacin) should be instituted, especially if clinical or ultrasonographic findings suggest occult pyelonephritis.

Confirming the Diagnosis of Diabetes Insipidus

Several different diagnostic approaches can be used to confirm central DI, nephrogenic DI, and primary (psychogenic) polydipsia. The water deprivation test is generally considered by most authorities to be the best diagnostic test to differentiate these disorders. However, the water deprivation test is labor intensive, is difficult to perform correctly, is unpleasant for the cat, relies heavily on repeated emptying of the bladder, and can lead to untoward complications and misdiagnosis in some cats.^{31,64,79}

A simpler and more practical method of diagnosis that can be recommended as an alternative to water deprivation testing is evaluation of the clinical response to a closely monitored therapeutic trial with the vasoressin analog, desmopressin.^{31,64,79} This approach is less complicated and time consuming than the water deprivation test and is certainly easier on the cat. The cost of the two approaches varies according to circumstances but is often comparable. Again, before a desmopressin trial is initiated, it is extremely important to rule out all other common causes of polyuria and polydipsia, limiting the differential diagnosis to central DI, primary nephrogenic DI, and primary (psychogenic) polydipsia.

To perform the test, the owner should first measure the cat's 24-hour water intake for 2 to 3 days before desmopressin is initiated, allowing free-choice water intake. The cat is then treated with therapeutic dosages of desmopressin (see the section on the *treatment of diabetes insipidus* later in this chapter), which ideally are administered subcutaneously at the dosage of 1.0 µg twice daily for a period of 5 to 7 days. If subcutaneous injections cannot be given, administration of desmopressin by the conjunctival (1 drop twice daily) or oral routes (75 mg twice daily) can be used (*Tables 24-13 and 24-14*). During this treatment period the owner should continue to measure the cat's daily water intake and monitor the degree of urine output.

A dramatic reduction in water intake (more than 50% of pretreatment measurements) and polyuria strongly suggests a diagnosis of central DI, whereas a lack of any reduction in polydipsia and polyuria is most consistent with primary nephrogenic DI. With more prolonged treatment, water consumption and urine output should completely normalize in cats with central DI.

TABLE 24-13 Desmopressin Formulations Available in the United States

Formulation	Concentration	How Supplied	Storage	Trade Name	Manufacturer
Nasal solution and sprays	0.1 mg/mL (100 µg/mL)	2.5-mL bottle	Refrigerate	DDAVP Rhinal Tube	Sanofi Aventis
	0.1 mg/mL (100 µg/mL)	5-mL bottle	Room temp	DDAVP Nasal Spray	Sanofi Aventis
	0.1 mg/mL (100 µg/mL)	2.5-mL bottle	Room temp	Minirin (DDAVP) Nasal Spray	Ferring Pharmaceuticals
	1.5 mg/mL (1,500 µg/mL)	2.5-mL bottle	Room temp	Stimate Nasal Spray	CSL Behring
	0.1 mg/mL (100 µg/mL)	5-mL bottle	Refrigerate	Desmopressin Acetate Nasal Soln (generic)	Bausch and Lomb
	0.1 mg/mL (100 µg/mL)	5-mL bottle	Room temp	Desmopressin Acetate Nasal Soln (generic)	Apotex Corporation
Injectable	4 µg/mL	1-mL single-dose vial 10-mL multiuse vial	Refrigerate	DDAVP Injection	Sanofi Aventis
	4 µg/mL	1-mL vial	Refrigerate	Minirin injection	Ferring Pharmaceuticals
	4 µg/mL	1-mL vial	Refrigerate	Desmopressin Acetate Injection (generic)	Hospira
	4 µg/mL	1-mL vial	Refrigerate	DDAVP injection (generic)	Teva Pharmaceuticals
Tablets	0.1 mg; 0.2 mg	Bottle of 100 tabs	Room temp	DDAVP Tablets	Sanofi Aventis
	0.1 mg; 0.2 mg	Bottle of 30 tabs	Room temp	Minirin Tablets	Ferring Pharmaceuticals
	0.1 mg; 0.2 mg	Bottle of 100 tabs	Room temp	DDAVP Tablets (generic)	Teva Pharmaceuticals
	0.1 mg; 0.2 mg	Bottle of 100 tabs	Room temp	Desmopressin Acetate Tablets (generic)	Apotex Corporation
Melt	60 mg; 120 mg; 240 mg	10, 20, or 100 wafers	Refrigerate	Minirin Melt®	Ferring Pharmaceuticals

Company websites for more information:

Sanofi Aventis: <http://www.sanofi-aventis.us/live/us/en/layout.jsp?scat=BD0DB735-32D7-41C4-898F-74F67D343145>

Ferring Pharmaceuticals: <http://www.ferring.com/en/therapeutic/urology/Products.htm>

[http://www.mims.com/Page.aspx?menuid=mng&name=Minirin+\(DDAVP\)+nasal+spray&CTRY=TW&brief=false](http://www.mims.com/Page.aspx?menuid=mng&name=Minirin+(DDAVP)+nasal+spray&CTRY=TW&brief=false)

CSL Behring: <http://www.stimate.com/>

Bausch and Lomb: http://www.bausch.com/en_us/msds/msds_listing.aspx

Hospira: <http://www.hospira.com/default.aspx>

Teva Pharmaceuticals: <http://www.tevusa.com/>

Apotex Corporation: <http://www.apotex.com/us/en/>

Desmopressin acetate is also available generically (many companies) and may also be known by the following synonyms and internationally registered trade names: Concentraid, D-Void, Defirin, Desmogalen, Desmospray, Desmotabs, Emosint, Minurin, Nocutil, Octim, Octostim, or Presinex.

TABLE 24-14 Treatment with Desmopressin in Cats

Formulation	Concentration	Route of Administration	Expected Daily Dose	Frequency of Administration	Cost of Generic Product
Nasal spray or solution	0.1 mg/mL (100 µg/mL)	Conjunctival drops	2-4 medium to large drops	Once daily or given every 8 or 12 hours	Intermediate (\$1.50-\$3.00/day)
Nasal spray or solution	0.1 mg/mL (100 µg/mL)	Subcutaneous	2-4 µg/day	Once daily or given every 12 hours	Cheapest (\$0.60-\$1.20/day)
Injectable solution	4 µg/mL	Subcutaneous	2-4 µg/day	Once daily or given every 12 hours	Most expensive (\$12-\$24/day)
Oral tablet	0.1 mg or 0.2 mg (100 µg and 200 µg)	Oral	50-150 µg/day	Given every 8 or 12 hours	Expensive (\$3.50-7.50/day)

In any older cat that develops DI, the veterinarian should consider pituitary imaging with CT or MRI to exclude a pituitary mass. This is especially true if the affected cat has associated neurologic signs.

Treatment of Diabetes Insipidus

Treatment with arginine vasopressin (the cat's ADH) or its analogs restores medullary hypertonicity and a normal urinary concentrating ability in cats with central DI. Historically, ADH tannate in oil, an extract of arginine vasopressin prepared from bovine and porcine pituitary glands, was administered every 2 to 3 days as needed to control polyuria and polydipsia. Because this product is no longer available, desmopressin acetate, a synthetic analog of arginine vasopressin with prolonged and enhanced antidiuretic activity, has become the drug of choice for the treatment of central DI in cats.

Desmopressin acetate is available in preparations for intranasal, parenteral (injectable), or oral administration (see Table 24-13).

NASAL SPRAYS OR SOLUTIONS OF DESMOPRESSIN

The nasal formulations are supplied with two different delivery systems: either a spray pump or a rhinal tube delivery system (see Table 24-13) in which the desmopressin is "sprayed" or "blown" into the nose, respectively. Obviously, most cats will not tolerate either of these intranasal delivery methods. Drops placed in the conjunctival sac provide a more suitable alternative for cats.

With the rhinal tube delivery formulation (DDAVP Rhinal Tube, Sanofi Aventis), the desmopressin is packaged with a small, calibrated plastic catheter so that exact amounts of the drug can be measured and administered. The calibrated rhinal tube has four graduation marks that measure amounts of 0.05 mL, 0.1 mL, 0.1 mL, and 0.2 mL and thereby can deliver doses of 5 to 20 µg of desmopressin. Although this system allows for accurate dosing, it is awkward to use. In addition, because this rhinal tube delivery system is not available as a generic product, this formulation is quite expensive.

The most common intranasal formulations of desmopressin are marketed as nasal sprays or solutions equipped with a compression pump that delivers 10 µg of drug with each spray. For use in cats this spray bottle should be opened and the desmopressin solution transferred to a sterile vial; this dispensing vial then allows the user to place the desmopressin drops within the cat's conjunctival sac. These intranasal preparations of desmopressin are generally supplied as a concentration of 100 µg/mL; depending on the size of the drop, 1 drop of nasal solution corresponds to 1.5 to 4 µg of desmopressin. One highly concentrated nasal solution (1.5 mg/mL) is marketed for use in hemophilia (see Table 24-13), but it should not be used to treat cats with DI because of the strong likelihood of overdosage.

In most cats 1 to 2 drops of the intranasal preparation administered once or twice daily are sufficient to control polyuria and polydipsia (see Table 24-14). Use of a tuberculin or insulin syringe allows for more accurate dosing. Application of desmopressin into the conjunctival sac may cause local irritation because the solution is acidic. Some cats may object to the daily eye drops, making this route of administration ineffective.^{4,81}

ORAL DESMOPRESSIN TABLETS

The oral preparation of desmopressin is available both as a sublingual dissolve melt tablet (not suitable for treating cats) and as 0.1-mg and 0.2-mg tablets. Each 0.1-mg (100-µg) tablet is roughly comparable to 5 to 10 µg (1 or 2 large drops) of the nasal solution (see Table 24-13). In one report of five cats with DI,⁴ all were treated successfully with oral desmopressin. Doses were variable, but most were well-controlled using oral dosages of 50 µg administered twice or three times daily.

The tablet form of desmopressin is a more cost-prohibitive alternative than the conjunctival or subcutaneous routes of administration. The cost of daily oral desmopressin in cats is roughly 2.5 times that of the cost of conjunctival drops and roughly 6 times the cost of subcutaneous injections of desmopressin. For some cat owners, however, the use of a tablet form may prove to be a more convenient, or the only possible, route of administration.

INJECTABLE DESMOPRESSIN SOLUTIONS FOR SUBCUTANEOUS OR INTRAVENOUS USE

An injectable sterile solution of desmopressin acetate (4 µg/mL) marketed for intravenous use is available (see Table 24-13) and can be used in cats with DI. However, the cost of the injectable desmopressin is approximately 7 to 15 times higher per µg than the intranasal preparation, making this formulation cost prohibitive for use in most cats. To circumvent this cost issue, the intranasal form of desmopressin—although not designed for parenteral use—can be given subcutaneously to cats with excellent results.^{14,16,43,81} Because the nasal forms of desmopressin are not considered to be sterile, however, it is best to first sterilize the product by passing the nasal solution through a 0.2-micron bacteriostatic syringe filter^{31,63} (see www.whatman.com/GDXSyringeFilters.aspx for more information). Clinically the nasal and injectable preparations of desmopressin induce indistinguishable responses when administered subcutaneously.

To make dosing easier, the desmopressin is best administered with an U-100 low-dose insulin syringe. The solution can be diluted in sterile physiologic saline to make dosing easier.

The subcutaneous route of desmopressin administration has many advantages over the other routes of

administration. These advantages include the following:

- First, drug appears to be most effective when administered via the subcutaneous route.
- Second, the duration of action is longer after subcutaneous injection than when administered orally or through the conjunctival sac.
- Third, because of the smaller subcutaneous doses required to control signs (about 15% and 40% of the oral and conjunctival doses, respectively), the cost of treatment is greatly reduced.
- Fourth, many cats seem to prefer long-term subcutaneous injections to the chronic use of eye drops or oral medication.

DOSE ADJUSTMENTS FOR DESMOPRESSIN

Recommended initial doses of desmopressin vary depending on the route by which it is being administered. If the conjunctival route is employed, 1 or 2 drops of the intranasal preparation administered once or twice daily is usually sufficient to control polyuria (see Table 24-14). With the subcutaneous route of administration, the initial recommended dose is 1 to 2 µg once or twice daily. If the nasal solution (100 µg/mL) were used for this purpose, the veterinarian would inject only 0.01 to 0.02 mL (or 1 to 2 U with a U-100 insulin syringe). With the oral tablets a starting dose of 0.05 µg to 0.075 µg (50 to 75 µg) once or twice daily is initiated.

In cats with central DI, daily administration of desmopressin may completely eliminate polyuria and polydipsia. However, because of individual differences in absorption and metabolism, the dose required to achieve complete, around-the-clock control varies from patient to patient. The maximal effect of desmopressin occurs from 2 to 8 hours after administration, and the duration of action varies from 8 to 24 hours.^{31,63} Larger doses of the drug appear to both increase its antidiuretic effects and prolong its duration of action; however, expense can become a limiting factor for some owners.

No matter what route of administration is used, the daily dose should be gradually adjusted as needed to control signs of polydipsia and polyuria. The morning and evening doses can be adjusted separately if needed.

ADVERSE EFFECTS OF DESMOPRESSIN

Desmopressin is relatively safe for use in cats with central DI. Adverse effects of desmopressin are uncommon, but overdosage can lead to fluid retention, hyponatremia, and decreased plasma osmolality.^{31,63} Although extremely rare, fluid intoxication associated with desmopressin overdosage can lead to central nervous system disturbances, including depression, increased salivation, vomiting, ataxia, muscle tremors, coma, and convulsions.^{31,41} In such instances furosemide can be given to induce diuresis.

To avoid the potential problem of overdosage, cats should not be allowed free access to water immediately after each dose of desmopressin, especially if severe polydipsia and polyuria have redeveloped. Without such short-term (1 to 2 hours) water restriction, the cat may consume excessive amounts of water that cannot be subsequently excreted, insofar as the desmopressin is absorbed and has its peak antidiuretic effects on the renal tubules.

COST OF DESMOPRESSIN

The principle drawback with the use of any of the desmopressin preparations in the treatment of central DI is the drug's considerable expense. The oral route of administration is the most expensive, and the subcutaneous route of administration (using the sterilized nasal solutions) is generally the most cost-effective.

Prognosis of Diabetes Insipidus

In some cats with DI, the owner may elect not to treat the cat because of financial concerns. Because polyuria and polydipsia do not pose a serious health hazard in these cats (as long as adequate access to water is available), treatment is not essential or mandatory. In cats with untreated DI, however, it is imperative that the water never be restricted because the inability to concentrate urine may lead to dehydration and possibly even death from neurologic complications.

Cats with idiopathic, traumatic, or congenital DI usually respond well to treatment with desmopressin, with near complete resolution of clinical signs of polyuria and polydipsia. With proper care these cats have an excellent prognosis and a normal life expectancy.

In contrast, cats with DI caused by large or aggressive hypothalamic masses or pituitary macrotumors have a grave prognosis. External radiation therapy in combination with desmopressin medical treatment offers the best chance for decreasing tumor size while controlling signs of polyuria in such cats.^{50,91} Fortunately, this appears to be an extremely rare cause of DI in cats.

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DISORDERS OF CALCIUM METABOLISM

Randolph M. Baral

CALCIUM HOMEOSTASIS

Calcium plays a key role in many physiologic processes. In addition to skeletal support, these include muscle contractions (skeletal, smooth, and cardiac muscle), transmission of nerve impulses, and blood clotting.⁴¹

In most cases plasma or serum biochemistry analytes are assessed by determining where the analyte is produced and excreted, as well as taking into account other influences. For example, albumin is produced by the liver and excretion is by way of renal or gastrointestinal routes. This means that in most cases a decrease in albumin is due to decreased production (indicating hepatopathy) or increased loss (due to renal or gastrointestinal causes). A further influence is dehydration, which can increase albumin results. In contrast to albumin, calcium regulation is exceedingly complex. In the first instance routine measurements of plasma or serum calcium are of total calcium (tCa), but calcium exists in three forms⁸³:

1. Ionized (free) calcium (iCa), which is the only physiologically active form and makes up 50% to 60% of tCa
2. Protein-bound calcium that accounts for approximately 10% of tCa
3. Complexed calcium (bound to e.g., phosphate, bicarbonate, lactate), which makes up 30% to 40% of tCa

Ionized calcium (iCa) must be measured immediately in-house or collected and separated anaerobically and measured within 2 hours (at room temperature) or 6 hours (if kept refrigerated).⁷

Our measurements of calcium are a reflection of extracellular fluid (ECF) calcium levels. The influences on ECF calcium are shown in Figure 24-30. Not only is ECF calcium increased by absorption from the gastrointestinal tract and decreased by secretion back to the gastrointestinal tract for excretion (90%), but filtration occurs through the kidneys for urinary excretion (10%). The kidneys also reabsorb 99% of this filtered calcium. Further, approximately 99% of total body calcium is stored in bones, which act as reservoirs, releasing calcium when ECF calcium reduces.⁴¹

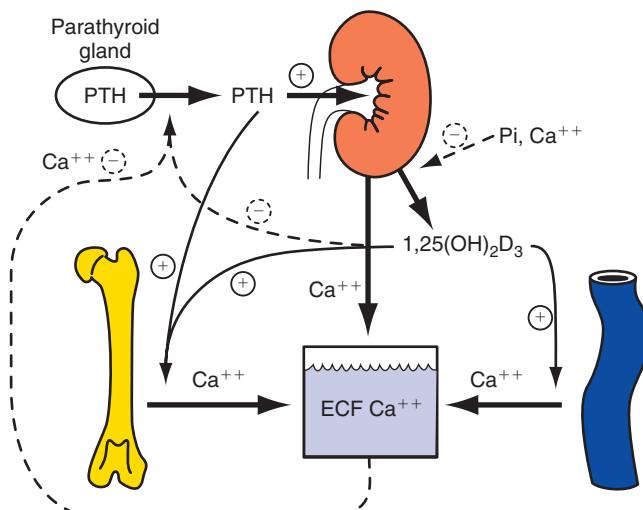


FIGURE 24-30 Influences on calcium concentrations. Extracellular fluid calcium is increased by absorption from the gastrointestinal tract, released from bone (where 99% of body calcium is stored) and reabsorbed by the kidneys. Extracellular fluid calcium reduces by secretion back to the gastrointestinal tract for excretion (90%) and filtration through the kidneys for urinary excretion (10%). These interactions are mediated by parathyroid hormone and calcitriol (activated vitamin D). Parathyroid hormone responds to decreased ionized calcium. Parathyroid hormone release results in increased calcitriol production by the kidneys. (From Schenck PA, Chew DJ, Behrend EN: Update on hypercalcemic disorders. In August JR, editor: Consultations in feline internal medicine, ed 5, St Louis, 2006, Elsevier Saunders, p 157.)

These interactions between the gastrointestinal tract, kidneys, and bone to maintain ECF calcium within a relatively narrow range are predominantly mediated by the following⁴¹:

1. Parathyroid hormone (PTH)
 - Produced by “chief cells” within the parathyroid gland
2. Calcitriol, or 1,25-dihydroxycholecalciferol, the most active form of vitamin D
 - The final stage of the conversion of vitamin D to calcitriol occurs within the kidneys
3. Calcitonin
 - Secreted by the thyroid gland
 - Has only a minor role in decreasing plasma calcium concentration

PTH acts to increase ECF calcium, and in a normal cat PTH is secreted in response to decreased levels of ECF calcium (or increased phosphate) and results in the following⁴¹:

1. Increased calcium (and phosphate) absorption from bone
2. Decreased calcium excretion from the kidneys (and increased phosphate excretion)
3. Increased calcitriol formation by the kidneys

Increased calcitriol levels result in the following⁴¹:

1. Increased intestinal absorption of calcium (and phosphate)
2. Enhancement of the ability of PTH to resorb bone
3. Decreased renal calcium and phosphate excretion (minor effect)

All these interactions are also influenced by plasma phosphate (PO_4) concentrations.⁴¹

APPROACH TO THE CAT WITH HYPERCALCEMIA

The clinical signs of hypercalcemia are very nonspecific. Mild hypercalcemia may not result in any signs. More severe clinical signs are usually associated with a concurrent problem (e.g., malignancy). Extreme hypercalcemia can cause depression of the nervous system, polyuria and polydipsia may be seen, and uroliths can form. A list of the clinical signs of hypercalcemia is shown with the pathophysiologic reason in Table 24-15. Mostly, however, hypercalcemia is detected by plasma biochemistry screening of a generally unwell cat with nonspecific signs such as lethargy or inappetence.

The following approaches to a cat with hypercalcemia must take into account physical examination and other laboratory findings as well as the cat's signalment (e.g., neoplasia is much less likely to occur in a kitten) and clinical history (e.g., possible exposure to rodenticide).

The main diagnostic steps are as follows:

1. Confirm finding of elevated tCa.
2. Measure iCa.
3. Measure PTH.
4. Measure parathyroid hormone-related protein (PTHrP) and vitamin D metabolites.
5. Assess results and relationships of tCa, iCa, and PTH concentrations.

Assessment of the results of these tests narrows down the potential causes of hypercalcemia considerably, particularly when the cat's age, clinical history, and physical examination findings are taken into account. Step 4, testing for vitamin D metabolites (calcidiol and calcitriol) and PTHrP should be considered as an optional step. The results of these tests are sometimes helpful, but a diagnosis can often be reached without testing for these. Together with further diagnostics, these will be discussed under the specific conditions where their testing is appropriate.

Step 1: Confirm Finding of Elevated Total Calcium

The tCa is usually measured by a colorimetric assessment and so is susceptible to spurious increases caused

TABLE 24-15 Clinical Signs of Hypercalcemia

Clinical Sign	Pathophysiology
Polyuria and polydipsia	Impaired response of renal tubules to antidiuretic hormone Impaired renal tubular resorption of sodium and chloride Secondary to renal damage
Weakness, depression, mental dullness	Depressed excitability of muscular and nervous tissue
Anorexia, vomiting, constipation	Decreased contractility of the smooth muscle of the gastrointestinal tract
Muscle twitching, shivering, seizures	Direct effect on central nervous system
Cardiac arrhythmias	Direct neurologic effect
Lower urinary tract signs	Presence of uroliths

Modified from Barber PJ: Disorders of calcium homeostasis in small animals, *In Pract* 23:262, 2001

by lipemia or hemolysis. Additionally, mild hypercalcemia may be transient. A second sample should be taken after a 12-hour fast because food intake can sometimes cause mild hypercalcemia, as well as lipemia. If the finding of hypercalcemia is repeatable, then iCa should be measured. Further, iCa can be increased when tCa is normal. In these cases tCa will be at the high end of the normal reference range, so it is appropriate to test iCa concentrations in those cats with repeatable high normal tCa concentrations.⁸⁵ It is prudent to collect a sample with the special handling required for iCa (discussed later) at the time of sampling for confirmation of elevated tCa.

Correction equations that take into account total protein or albumin levels have been devised for people and dogs to improve diagnostic interpretation of tCa values.^{55,62} These equations are controversial in these two species. In cats the equations are even less reliable because the relationship between tCa and albumin is too variable.³⁷

Step 2: Measure Ionized Calcium

The iCa should be measured in all cases where tCa is elevated or on the high side of the normal reference range. iCa values can be artefactually increased by exposure to air because pH and temperature affect the equilibrium between the three fractions of ionized, protein-bound, and complex-bound calcium.^{7,85} Therefore samples should be tested immediately with an in-house analyzer or collected anaerobically and sent chilled (4° C) to a commercial laboratory.

When heparinized whole blood is used for in-house iCa sampling, it results in a lower iCa concentration than

serum samples.⁴⁰ These differences should be taken into account by using different reference ranges. Commercial laboratories measure iCa from serum. Ethylenediaminetetraacetic acid (EDTA) plasma must never be used for either in-house or commercial laboratory assessment of ionized calcium because EDTA chelates calcium, which falsely reduces the concentration.⁸⁵

Anaerobic collection of serum requires two serum vacutainer tubes, a centrifuge, and a spinal needle. Silicon separator vacutainer tubes should not be used because calcium is released from the silicone gel, falsely elevating the calcium level. The needle of the syringe used to collect the blood sample from the cat should be placed directly through the stopper of the first vacutainer tube (without opening the tube) to transfer the sample from syringe to blood tube. The blood should be allowed to clot (approximately 20 minutes), then separated by centrifugation. The spinal needle (attached to a syringe that does not contain air) is used to withdraw serum from this tube without opening it. This serum is then transferred to the second vacutainer tube (again, without opening the tube). The sample is refrigerated and then sent to the reference laboratory with an ice pack.⁸³

Step 3: Measure Parathyroid Hormone

PTH is an 84-chain amino acid. The amino acid sequence of PTH is known for the dog, cow, pig, rat, chicken, and human, and most mammals appear to have very similar amino-terminal portions of the molecule.⁸⁷ Mature feline PTH is 84% identical to human PTH.⁹⁷ At least two PTH assays have been validated for use in the cat. Both are two-site immunoradiometric assays (IRMA) for human intact PTH. *Two-site* means using antibodies that bind with epitopes at the two terminals of the molecule and therefore avoids measuring the PTH fragments that can be present in blood and would otherwise potentially be detected by a one-site assay (rendering it less accurate).^{10,77} Serum or plasma can be assayed but should be separated with minimal exposure of samples to room temperature (less than 2 hours). The samples then should be refrigerated or frozen before analysis to prevent degradation.^{6,85,87}

The serum sample for iCa requires similar handling. It is therefore practical to use the same serum for both iCa and PTH at a reference laboratory.

Step 4: Measure PTH-Related Protein and Vitamin D Metabolites

PTHrP is secreted by some malignant neoplasms and mimics the action of PTH by binding to PTH receptors. It is elevated in some cases of hypercalcemia of malignancy, but not all. One study of 322 cats with elevated iCa found PTH in the lower half of the normal reference range in 263 cats (81.7%), yet PTHrP was elevated in

only 31 cats (9.6%). Clinical records were not available for all cats, and only seven cats had confirmed malignancy.⁷⁷ It is highly likely that a large number of cats with normal PTHrP had hypercalcemia caused by malignancy.

Two-site assays for human PTHrP have been validated for cats.⁷⁷ PTHrP is best measured from fresh or frozen EDTA plasma.⁸⁴

Vitamin D metabolites are identical in all species, so radioimmunoassays used for humans are appropriate for cats.⁸⁴ Human endocrinology laboratories often offer this testing, and developing a relationship with such a laboratory at a local human hospital can be beneficial for practitioners. The different vitamin metabolites should be considered. Calcidiol (25-hydroxyvitamin D) increases with ingestion of cholecalciferol-containing rodenticides. Calcitriol (1,25-dihydroxyvitamin D) increases with ingestion of calcitriol-containing plants (such as *Cestrum diurnum* [day-blooming jessamine]) and granulomatous inflammation. Calcidiol and calcitriol are best measured from chilled serum. Neither analyte is increased with hypercalcemia caused by ingestion of calcipotriene, a vitamin D analog found in psoriasis cream.⁸⁴

Step 5: Assess tCa, iCa, and Parathyroid Hormone Relationships

Table 24-16 outlines common conditions that result in hypercalcemia together with the tCa, iCa, PO₄, and PTH results. Broadly, disorders resulting in hypercalcemia should be classified as those for which PTH is typically increased, those for which PTH is typically reduced, and those for which PTH is normal. Exceptions to these findings do occur, and these are addressed under the specific conditions. The most common causes of hypercalcemia in cats, with the most common iCa and PTH findings, are as follows:

1. Neoplasia:
 - iCa often very high
 - PTH often undetectable, may be in lower half of reference range
2. Renal disease:
 - iCa often normal
 - PTH elevated
3. Idiopathic hypercalcemia
 - iCa often mildly elevated
 - PTH in lower half of normal range

Mnemonics, such as "GOSH DARN IT"⁸⁵ for all causes of hypercalcemia and "SHIRT"²⁴ for common causes of hypercalcemia have been devised. These are listed in Boxes 24-5 and 24-6. Veterinarians are advised to remember the causes of hypercalcemia in terms of PTH results because this gives a better understanding of the underlying processes.

TABLE 24-16 Common Conditions That Result in Hypercalcemia with Expected Calcium (Total and Ionized), Albumin, Phosphate, Parathyroid Hormone, and Other Calcemic Indices*

	tCa	iCa	Alb	PO ₄	PTH	PTHrP	25-OH vit D	1,25(OH) ₂ vit D
INCREASED PTH								
Primary hyperparathyroidism	↑	↑	N	↓ or N	↑	N	N	N or ↑
Renal secondary hyperparathyroidism	↑	N or ↓	N	↑	↑	N	N or ↓	N or ↓
Tertiary hyperparathyroidism	↑	↑	N	↑	↑	N	N or ↓	↓ or N
REDUCED PTH								
Neoplasia Humoral hypercalcemia	↑	↑	N or ↓	↓ or N	↓ or N	↑ or N	N	↓ or N or ↑
Neoplasia Local osteolytic	↑	↑	N or ↓	N or ↑	↓ or N	N or ↑	N	N
Hypervitaminosis D Calcitriol (including granulomatous inflammation)	↑	↑	N	N or ↑	↓	N	N	↑
Hypervitaminosis D Cholecalciferol (rodenticide)	↑	↑	N	↑ or N	↓	N	↑	N or ↑
NORMAL PTH								
Idiopathic	↑	↑	N	N or ↑	N or ↓	N	N	N or ↓ or ↑
MISCELLANEOUS CAUSES								
Dehydration	↑	N or ↑	↑ or N	N or ↑	N or ↓	N	N	N
Hypoadrenocorticism	↑	↑	N or ↓	↑ or N	↓ or N	N	N	↓ or N
Hyperthyroidism	N or ↑ or ↓	↑ or ↓	N	N or ↑	↑ or N or ↓	N	N	N or ↓

tCa, Total calcium; iCa, ionized calcium; alb, albumin; PO₄, phosphate; PTH, parathyroid hormone; PTHrP, PTH-related peptide; 25-OH vit D, calcidiol; 1,25(OH)₂ vit D, calcitriol; N, normal.

*Note that the most common conditions are highlighted yellow. Variations in expected results are indicated with the more common result noted first.

BOX 24-5

“GOSH DARN IT” Mnemonic to Help Remember Causes of Hypercalcemia

- Granulomatous disease
- Osteolysis
- Spurious (e.g., laboratory error; presence of lipemia, hemolysis)
- Hyperparathyroidism, House plant ingestion, Hyperthyroidism
- D toxicosis (i.e., vitamin D toxicosis), Dehydration
- Addison’s disease (hypoadrenocorticism), Aluminum toxicity
- Renal disease
- Neoplasia, Nutritional
- Idiopathic
- Temperature (hyperthermia)

Modified from Schenck PA, Chew DJ, Behrend EN: Update on hypercalcemic disorders. In August JR, editor: *Consultations in feline internal medicine*, ed 5, St Louis, 2006, Elsevier Saunders, p 157.

BOX 24-6

“SHIRT” Mnemonic to Help Remember Common Causes of Hypercalcemia

- Spurious (lipemia, hemolysis; always verify before proceeding)
- Hyperparathyroidism
- Idiopathic
- Renal disease (mostly normal iCa despite elevated tCa)
- Tumors (lymphoma, carcinoma, multiple myeloma)

Modified from Cook AK: Guidelines for evaluating hypercalcemic cats, *Vet Med* 103:392, 2008.

INCREASED PARATHYROID HORMONE WITH HYPERCALCEMIA

Hypercalcemia with increased PTH may be due to primary hyperparathyroidism or renal secondary hyperparathyroidism. Tertiary hyperparathyroidism is a rare consequence of renal secondary hyperparathyroidism. Renal disease is a far more common cause of hypercalcemia than primary hyperparathyroidism. Hypercalcemia from renal disease usually results in increased tCa but normal iCa.

Primary Hyperparathyroidism

Primary hyperparathyroidism is relatively rare in cats. One case series of 71 hypercalcemic cats recognized only four cats with this condition.⁸² One small cases series of seven hyperparathyroid cats has been reported,⁵⁰ but all other publications have been case reports.* One case was reported in a cat with multiple endocrine neoplasia.⁷⁸ Further, nonfunctional parathyroid adenomas were removed from two cats, having been recognized by cervical palpation.⁶⁹ The underlying cause is commonly benign, such as adenoma, cystadenoma, or hyperplasia^{17,28,50,82,93} but can be malignant adenocarcinoma.^{50,57,75}

The age range of affected cats was 8 to 20 years, with no sex predisposition. There are no definitive breed predispositions; five of the seven initial cases were Siamese,⁵⁰ most subsequent cases have been mixed-breed cats, but two recent cases were Persian.^{2,19}

Presenting clinical signs are generally nonspecific and consistent with hypercalcemia of any cause (see Table 24-15); polydipsia and polyuria do not seem to be commonly reported. Physical examination findings are generally nonspecific; however, a palpable parathyroid (that may be mistaken for an enlarged thyroid gland) may be present in approximately 40% of cases. One cat with probable primary hyperparathyroidism had lytic changes and disruption of normal bone architecture, affecting mainly the femoral diaphyses.³⁹

Laboratory results show elevations of tCa and iCa with an inappropriately elevated PTH concentration; phosphate is suppressed by PTH and so should initially be low but may rise with impaired renal function caused by ongoing hypercalcemia. In a physiologically normal cat, hypercalcemia should suppress PTH, so a PTH concentration at the high end of the normal reference range may still suggest primary hyperparathyroidism. Further, PTH concentrations vary with time. In one case five of seven PTH measurements from the same cat were normal; the other two were notably increased.²⁸

Ultrasound has been used as a diagnostic aid in some cases.^{75,93} In one report parathyroid adenomas in two cats measured greater than 1 cm in diameter and contained hypoechoic regions with distal acoustic enhancement, compared to the hyperechoic homogeneous masses.⁹³ In another case fluid retrieved by fine-needle aspiration from a cystic cervical mass had higher concentrations of PTH than serum from the same cat.⁷⁵

Surgical resection of the abnormal parathyroid tissue is the treatment of choice. Before surgery, it is advisable to use fluid therapy to rehydrate the animal and attempt to reduce the severity of the hypercalcemia. Surgical approaches are as for thyroidectomy (see the section on [Thyroid Gland Disorders](#)). During surgery, the ventral and dorsal surfaces of both thyroid and parathyroid complexes should be examined. Any enlarged or discolored parathyroid tissue should be removed. Parathyroid adenomas are usually single nodules, and the remaining normal tissue is typically atrophied and can be difficult to see. However, in some cases, adenomas may be as small as 2 mm in diameter. External parathyroid adenomas are easily removed, but excision of adenomas of internal parathyroid glands may require removal of the entire thyroid and parathyroid complex on that side. It is imperative that at least one parathyroid gland is left intact to prevent permanent hypoparathyroidism. If no abnormal parathyroid gland tissue can be visualized, it is possible that an ectopic parathyroid gland is responsible. A thorough inspection of the ventral neck should be made, although an ectopic gland may be located in the cranial mediastinum. In most cases the abnormal parathyroid gland will be palpated before surgery, making the procedure relatively straightforward.⁷

Because chronic hypercalcemia leads to atrophy of normal parathyroid glands, surgical removal of the autonomously secreting gland will lead to a rapid decline in PTH levels and relative hypoparathyroidism.⁶ It is therefore crucial to monitor closely for signs of hypocalcemia. Hypocalcemia that is sufficiently severe to require treatment is likely to develop within 24 to 48 hours, with clinical signs of hypocalcemia occurring 3 to 6 days after surgical removal of a parathyroid gland tumor.⁸⁷ Most reported cases have been treated preventively with calcitriol and calcium to reduce this risk, but hypocalcemia has not been a commonly recognized sequela.^{28,50,51} Initiating treatment for hypocalcemia before the onset of clinical signs is not recommended because it removes the hypocalcemic stimulus to reverse parathyroid atrophy by actively inhibiting PTH secretion.⁶ If hypoparathyroidism does result after surgery, it is usually transient, and treatment can be gradually withdrawn over a few months. In some cases the postoperative stabilization of serum calcium can present a major challenge.⁷

*References 2, 17, 19, 28, 39, 51, 57, 75, 93.

Renal Disease

Chronic renal disease (CRD) is one of the more common underlying causes of hypercalcemia in cats.^{82,85} The frequency of hypercalcemia among cats with CRD has been reported from 11.5%²⁹ to 58%,⁹ but the author recognizes far fewer than even this lower number. The degree of hypercalcemia correlates with the severity of renal disease; in one study of 73 cats with CRD, the frequency of hypercalcemia was 8% in cats with compensated renal disease, 18% in those with uremic renal disease, and 32% in cats with end-stage renal disease (that died within 21 days of sampling).⁹

Hypercalcemia caused by CRD often results in normal to low iCa, but occasionally iCa can be elevated.^{9,85} Therefore normal to low iCa concentrations make underlying CRD more likely, but an elevated iCa concentration does not rule out CRD.

Insofar as hypercalcemia can cause CRD, the presence of both concomitantly creates a diagnostic challenge. Hypercalcemia *caused by* renal failure is usually quite mild. The primary cause is phosphate retention resulting from the failing kidneys' inability to secrete sufficient phosphate, leading to PTH secretion. Other mechanisms are also responsible, including alterations to serum protein binding and decreased GFR.⁴¹ In most cases tCa will be increased but iCa will be normal or low (the increase in tCa being related to altered protein binding)—if this is the case, it is easier to resolve the etiology (renal failure causing the hypercalcemia), and the lack of ionized hypercalcemia means that specific therapy is not required.

Deleterious effects of hypercalcemia occur in patients with CRD only if it is associated with increases in serum iCa concentration. Consequently, clinical signs of hypercalcemia are uncommon in CRD patients, and measurement of serum iCa concentration to assess calcium status in CRD patients is important.

Tertiary hyperparathyroidism has been recognized for some time in humans. The term refers to the emergence of ionized hypercalcemia over months to years as a result of progression from renal secondary hyperparathyroidism. Consequently, the patient has elevated tCa, iCa, and PTH because of an alteration in the calcium set point to stimulate release of PTH (i.e., higher concentrations of iCa are necessary to inhibit PTH secretion).²⁶ As already noted, elevated iCa is sometimes recognized in cats with hypercalcemia caused by CRD⁹; however, tertiary hyperparathyroidism has not specifically been described in cats.

Prevention of phosphate retention is central to the management of CRD and has been shown to reduce renal secondary hyperparathyroidism.¹¹ Treatment consists primarily of dietary phosphate restriction using phosphate-restricted diets or intestinal phosphate-binding agents (or a combination of the two, if required).

There is a small chance that phosphate-restricted diets or phosphate binders can actually cause hypercalcemia. In one study 2 of 15 cats with CRD developed hypercalcemia while eating a phosphate-restricted veterinary diet designed for treatment of CRD. Hypercalcemia in these cats was associated with a decrease in serum phosphorus and low or undetectable PTH concentrations. Hypercalcemia resulted in clinical signs for one cat. In this cat the dietary therapy was stopped for 6 months. The phosphate-restricted diet was then reintroduced such that the cat was fed two thirds of its energy intake as phosphate-restricted diet and one third as ordinary commercial canned cat food, which halted the rise in plasma phosphate and PTH. The proportion of phosphate-restricted diet was subsequently increased and this reduced plasma phosphate and PTH concentrations to below pretreatment values without recurrence of the hypercalcemia. The other cat showed no clinical signs of hypercalcemia, and calcium returned to normal on cessation of the phosphate-reduced diet.¹¹

Theoretically, the agents in phosphate binders could cause hypercalcemia. The most commonly used phosphate binders for cats with CRD contain aluminum phosphate. Aluminum has been shown to experimentally cause hypercalcemia and renal disease in dogs.⁴³ Alternative phosphate binders for cats contain calcium carbonate. Calcium carbonate is also an ingredient of many antacids used for humans, and hypercalcemia has been recognized as a result of consumption of large amounts of such antacids.⁴² Hypercalcemia as a result of ingestion of aluminum hydroxide or calcium carbonate as phosphate binders has not been described in cats but is theoretically possible.

Therapy with low-dose calcitriol has been recommended as preventive management of renal secondary hyperparathyroidism in textbooks and review articles.^{21,67,68} One study of 10 cats showed that PTH concentrations were not significantly different after 14 days of calcitriol administration.⁴⁷ It is possible that a longer duration of therapy is required to note benefits. An unpublished 1-year-duration randomized, controlled clinical trial failed to show any benefit in cats with varying severity of CKD; the possibility that calcitriol was of benefit was not excluded by the study.⁷⁶ Of course, overdosing a cat with calcitriol used for this purpose can, in itself, result in hypercalcemia.

DECREASED PARATHYROID HORMONE WITH HYPERCALCEMIA

The most common reason for hypercalcemia associated with suppressed levels of PTH is neoplasia. In most cases PTH is suppressed to undetectable or very low concentrations (i.e., zero or approaching zero). On some occasions cats with hypercalcemia of malignancy may

have PTH concentrations in the middle of the normal reference range,⁷⁷ thus creating overlap with idiopathic hypercalcemic cats and potential diagnostic difficulties. An alternative diagnosis for suppressed PTH concentration is hypervitaminosis D, which can result from vitamin D ingestion or granulomatous inflammation.

In many cases there will be a clinical history of toxic ingestion, or potential neoplasia will be recognized at physical examination (e.g., palpation of an abdominal mass), and these overt signs should be investigated in the first instance. Further investigations of hypercalcemia are appropriate in cases when no such toxin exposure or indicative physical examination findings are present.

Distinctions may be found by measuring PTHrP or vitamin D metabolites. However, malignancy-associated hypercalcemia does not necessarily cause an increase in PTHrP, and the different forms of vitamin D create different responses depending on what the toxic agent is. PTHrP and vitamin D metabolite measurements may be considered relatively specific (false-positive results are unlikely) but not very sensitive (false-negative results are a strong possibility).

Neoplasia

Malignancy-associated hypercalcemia may result from two mechanisms:

1. Humoral hypercalcemia of malignancy (HHM)
 - Neoplastic tissues can elaborate numerous cytokines that act like PTH to stimulate bone resorption, thus elevating serum calcium
 - PTHrP is a principal mediator of this effect, but others are possible
2. Local osteolytic hypercalcemia
 - Subsequent to local invasion and dissolution of bone by the tumor

Numerous types of malignancies have been associated with hypercalcemia of malignancy. Most commonly reported is lymphosarcoma^{32,33,82} (in various locations) or squamous cell carcinoma^{48,54,82} (e.g., in the mandible or ear canal); hypercalcemia of malignancy has also been recognized with multiple myeloma,^{14,44,90} osteosarcoma,⁸² fibrosarcoma,⁸² bronchogenic carcinoma,⁸² leukemia,⁶⁰ renal carcinoma, and thyroid carcinoma.⁷⁷ The author has recently recognized hypercalcemia in a cat with intestinal small cell lymphoma. In many cases neoplasia will be apparent on physical examination. When hypercalcemia is recognized in a generally unwell cat and iCa is increased and PTH is very low or even unrecordable, investigations for neoplasia should take place. Increased concentrations of PTHrP indicate malignancy is present, but failure to detect increased PTHrP does not rule it out; calcidiol and calcitriol concentrations will be normal in most cases.

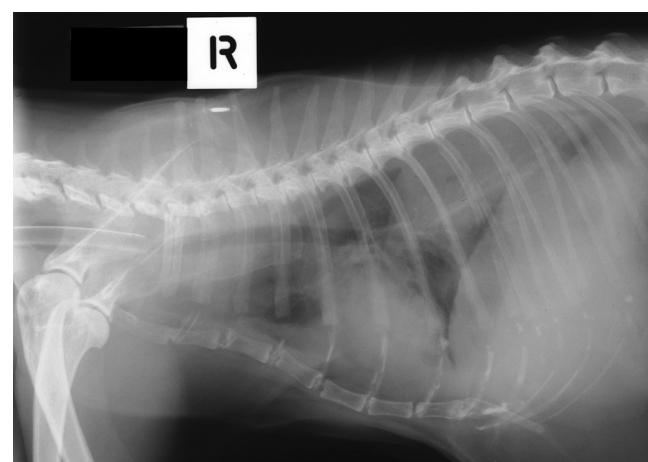


FIGURE 24-31 Lateral thoracic radiograph of a cat with hypercalcemia of malignancy caused by bronchogenic carcinoma. Note that there is not only pleural effusion and a consolidated caudal lung lobe but also osteolysis of the ninth rib. The tumor was also adhered to the diaphragm, so one diaphragmatic crus is farther cranial than the other.

Thoracic radiographs (Figure 24-31), abdominal ultrasonography, and bone marrow aspiration are all appropriate investigations. The order in which these are undertaken will depend on the clinical signs, but sometimes all three are necessary.

Treatment of malignancy-associated hypercalcemia requires treatment of the underlying malignancy; however, therapies to reduce the magnitude of hypercalcemia (discussed later) may be necessary. There are no data in cats to compare survival times of cats with neoplasia with and without hypercalcemia.

Hypervitaminosis D

Hypervitaminosis D is not very common in cats but is an important differential diagnosis for hypercalcemia of malignancy. As with malignancy, hypervitaminosis D results in elevated iCa and suppressed PTH. It is important to obtain a thorough clinical history with potential of ingestion of, or access to, known toxins (discussed later). Presence of an abdominal mass or intrathoracic lesions may indicate that the hypercalcemia is associated with granulomatous inflammation and not neoplasia. Serum calcitriol will be elevated in most cases of hypervitaminosis D (exceptions are noted later).

Granulomatous Inflammation

Hypercalcemia can result from granulomatous inflammation because macrophages can synthesize calcitriol from calcidiol without negative feedback regulation. Hypercalcemia has been recognized in cats with mycobacteriosis,^{5,61} nocardiosis,⁶¹ histoplasmosis,⁴⁵ toxoplasmosis, pulmonary cryptococcosis, *Actinomyces* rhinitis, and feline infectious peritonitis.⁸² A direct

association between granulomatous inflammation and hypercalcemia was not made in most reported cases, but elevated calcitriol concentrations were recognized in one cat with both nocardiosis and atypical mycobacterial infection.⁶¹

In most cases investigations will proceed to diagnose abnormalities found on physical examination and include thoracic radiographs and abdominal ultrasonography. Hypercalcemia may, in such cases, be wrongly considered to be due to neoplasia. An elevated calcitriol concentration can help distinguish such cases as being due to granulomatous inflammation rather than neoplasia. It is, however, theoretically possible for neoplasia to cause a granulomatous response sufficient to cause hypercalcemia; a definitive diagnosis of the cause of hypercalcemia requires cytologic or histologic assessment with culture required to identify the causative agent.

Toxic Exposures

Vitamin D toxicity is not commonly reported in cats because they seem to be resistant to cholecalciferol toxicosis if their diet is otherwise complete and balanced.⁹¹ However, several reports from Japan in the early 1990s documented significant hypercalcemia with clinical signs resulting from hypervitaminosis D associated with commercial diets consisting of fish that contained over 100 times the minimal requirement of cholecalciferol (50 IU/100 g of diet for growing cats).^{66,81}

Toxicity can occur from ingestion of vitamin D-containing plants such as *C. diurnum* (known as day-blooming cestrum, or day-blooming jessamine, or day-blooming jasmine).³¹ Calcitriol may be used to treat hypoparathyroidism and potentially renal secondary hyperparathyroidism, and overdosing (perhaps after an error by a compounding pharmacist) is another potential source of toxicity.⁸⁵ All these toxicities will result in an elevation of calcitriol (1,25-dihydroxyvitamin D) with normal calcidiol (25-hydroxyvitamin D).

Ingestion of cholecalciferol-containing rodenticides such as Quintox or Rampage^{65,72} can also cause hypervitaminosis D. In these circumstances calcidiol will be elevated, and calcitriol is often normal but may be elevated. Calcidiol can remain elevated for weeks to months because of lipid storage and slow release.⁸⁵

Calcipotriol or calcipotriene is a calcitriol analog formulated as a topical dermatologic agent to treat psoriasis in people. There are anecdotal reports of cats licking this ointment from their owners' skin⁸⁵ and documented cases of toxicity in dogs.^{18,34,80,98} With calcipotriol toxicity, calcidiol concentrations remain normal; calcitriol concentrations would be expected to remain normal (or perhaps be suppressed), but this is undetermined.⁸⁵

NORMAL PARATHYROID HORMONE WITH HYPERCALCEMIA

The main consideration for a cat with hypercalcemia and normal PTH concentration is idiopathic hypercalcemia. Because cats with hypercalcemia of malignancy may have PTH levels in the lower half of the normal reference range, there can be considerable overlap with cats with idiopathic hypercalcemia. Cats for which this diagnostic dilemma occurs (but in which occult neoplasia is not detected after thoracic auscultation, abdominal ultrasonography, and bone marrow analysis) should be managed as if they had idiopathic hypercalcemia. These cats also should be serially monitored (every 3 months is appropriate for a stable cat), not only for calcium concentrations but with a thorough examination on each visit with a clinical suspicion of neoplasia. Repeat ancillary testing to look for occult neoplasia is appropriate if clinical signs arise, but after a period of time (1 year can be considered a good yardstick), idiopathic hypercalcemia becomes more likely and the need for repeat diagnostics decreases.

Idiopathic Hypercalcemia

Idiopathic hypercalcemia refers to abnormally elevated serum iCa concentration of unknown cause after extensive medical evaluation to rule out known causes of hypercalcemia.²³ It may now be the most common type of hypercalcemia and has been anecdotally recognized in North America, Europe,²³ and Australia despite being reported only in the United States.^{63,88}

With idiopathic hypercalcemia serum calcium concentrations can be increased for months to years without overt clinical signs. Hypercalcemia may initially be recognized as a fortuitous discovery from a blood sample taken in a well cat (e.g., for preanesthetic screening) or a cat with an unrelated condition. One study reported as an abstract assessed 427 cats with idiopathic hypercalcemia recognized at a single diagnostic laboratory; no clinical signs were noted in 46% of cases, 18% had mild weight loss only, chronic constipation was noted in 5% of cats, and inflammatory bowel disease was seen in 6% (although it was not noted how this was diagnosed). Uroliths or renoliths were observed in 15% of cats, and calcium oxalate stones were specifically noted in 10% of cases.⁸⁸ Similarly, in an earlier series of 20 cases, 35% of cats had urolithiasis, as well as signs normally attributable to the gastrointestinal tract, such as vomiting and diarrhea.⁶³ The recognition of intestinal signs is interesting insofar as an association has been made between inflammatory bowel disease and renal urolith formation in humans (possibly because of poor absorption of magnesium and citrate, which are considered stone inhibitors).⁵⁹ No such association has been made in cats.

Cats with idiopathic hypercalcemia can be any age; the clinical cases series of 20 cats found an age range of 2 to 13 years (with a mean of 5.8 years)⁶³ compared with the larger set of 427 cats, which found a mean of 9.8 years (range 0.5 to 20 years).⁸⁸ No gender predispositions are recognized, but longhaired cats seem to be overrepresented, including both domestic longhaired cats and purebreds, such as Persians and Himalayans.^{63,88}

In most cases elevations of both tCa and iCa concentrations are mild to moderate (10% to 20% above the upper limit of the reference range), but some cats can have markedly high elevations. PTH concentrations are typically normal but at the low end of the reference range, with the mean value equaling 1.1 pmol/L (range 0 to 4) in both series.^{63,88} PTHrP was negative in 301 cats tested in one series⁸⁸ but increased in 1 of 11 cats in the other. The reason for the abnormally high concentration of PTHrP in this cat could not be determined, but the cat survived more than 3 years after the onset of hypercalcemia, making underlying malignancy an unlikely explanation for the high PTHrP concentration.⁶³ Calcitriol was normal in 12 cats in one series⁸⁸ but increased in one of seven cats in the other. Similar to the cat with increased PTH, this cat lived a further 2 years after the onset of hypercalcemia, and at postmortem examination neither neoplasia nor granulomatous disease was identified.⁶³

The relationship between renal disease and idiopathic hypercalcemia is not clear-cut. Renal disease can occur secondary to longstanding idiopathic hypercalcemia (Figure 24-32); some cats with renal disease can have idiopathic hypercalcemia recognized after protracted

periods of normocalcemia; in yet other cats, renal disease may be recognized concurrently with recognition of idiopathic hypercalcemia.⁸⁵

Multiple factors have been considered in relation to the underlying cause of idiopathic hypercalcemia. It is unknown whether increased intestinal calcium absorption, increased bone resorption, or decreased renal calcium excretion (or some combination thereof) is the key factor leading to the development of this condition.

Three of five cats in one series⁵⁸ and all 14 cats for which diet history was available in another⁶³ had been fed acidifying diets designed to minimize struvite crystalluria and urolithiasis. Of course, not all cats on acidifying diets develop hypercalcemia, so these patients must have had an additional underlying factor that predisposed them to hypercalcemia. All five cats in that first series⁵⁸ had reduced serum calcium when the diet was changed to a high-fiber diet, and two of four cats that could be assessed had a partial response in the second study.⁶³ Genetics is another consideration, given the overrepresentation of longhaired cats.

Management of idiopathic hypercalcemia is discussed in the following section.

OTHER CAUSES OF HYPERCALCEMIA

Some causes of hypercalcemia are not appropriate for assessment in relation to PTH levels—chiefly, hypercalcemia caused by endocrinopathies. In these cases the underlying condition dictates the clinical investigations and findings, and hypercalcemia is relatively mild and resolves as the underlying disease is managed.

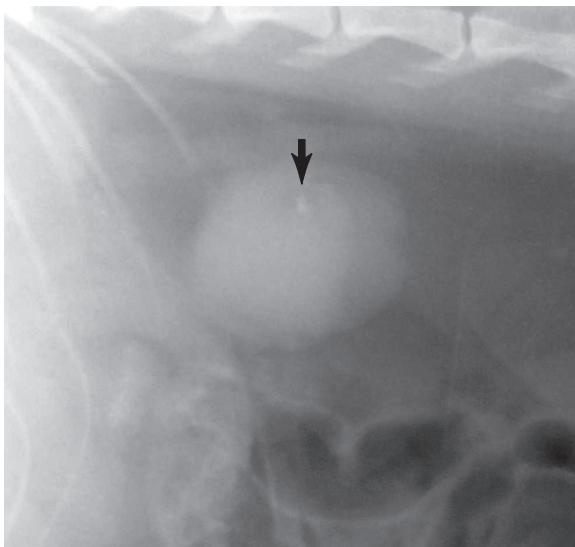


FIGURE 24-32 Small, misshapen kidneys as a consequence of idiopathic hypercalcemia. Note the small urolith (arrow). This cat's hypercalcemia with elevated ionized calcium and midrange parathyroid hormone was recognized more than 12 months before the development of azotemia.

Hyperthyroidism

One study has recognized increased tCa, but normal iCa, in 2 of 26 hyperthyroid cats,⁸ and a study of 71 hypercalcemic cats recognized 2 hyperthyroid cats.⁸² Conversely, decreased iCa concentrations can be seen, and increased PTH concentration was recognized in 77% of hyperthyroid cats in one of these reports.⁸ The reasons for and importance of these changes are not entirely clear. Hypercalcemia almost invariably resolves on treatment of hyperthyroidism.

Hypoadrenocorticism

Naturally occurring primary hypoadrenocorticism has been well documented in 18 cats (see the section on [Adrenal Gland Disorders](#)); of these, three cats (17%) were hypercalcemic. Additionally, one cat with iatrogenic hypoadrenocorticism and DM was hypercalcemic,⁹² and in a series of 71 hypercalcemic cats, one was hypoadrenocorticoid.⁸² The hypercalcemia in these

patients is usually mild and has little effect on the outcome of hypoadrenocorticism. The magnitude of hypercalcemia usually parallels the severity of hyperkalemia and hypovolemia. The mechanism of hypercalcemia is unknown and typically resolves with treatment of hypoadrenocorticism.⁸⁶

TREATMENT OF HYPERCALCEMIA

Acute Therapy

The principle treatment aim for a hypercalcemic cat is to identify and *manage the underlying condition*. Treatment to specifically reduce hypercalcemia may be necessary based on the degree of hypercalcemia or severity of clinical signs resulting from hypercalcemia. There is no absolute serum calcium concentration that can be used as a guideline for the decision to treat hypercalcemia aggressively, but a serum calcium concentration of 4 mmol/L (16 mg/dL) or greater has been recommended as a rule of thumb.⁸⁷ In practice, hypercalcemia of this magnitude can be expected to be accompanied by clinical signs such as depression, anorexia, vomiting, or dysrhythmia. Concurrent hyperphosphatemia potentiates soft tissue mineralization, and the result of multiplying serum calcium by serum phosphate (calcium × phosphate product) has been used to judge the risk of nephrotoxicity and thus help determine whether immediate treatment is required.⁸⁵ When using U.S. units (mg/dL), a calcium × phosphate product of 60 to 80 has been used as the level at which to consider treatment; this correlates to a calcium × phosphate product of approximately 5 to 6.5 when using SI units. The principles of emergency treatment of severe hypercalcemia are summarized in sequential order in **Box 24-7**.

Intravenous fluid therapy is the first step in symptomatic treatment of hypercalcemia. The initial aim is to correct fluid deficits, but the volume expansion not only dilutes the circulating calcium concentration but also increases renal calcium excretion. Normal (0.9%) saline is the fluid of choice and should be infused at approximately 2 to 3 times the maintenance requirements, which for most cats means 20 to 30 mL per hour. Potassium supplementation is usually required, and maintenance potassium requirements can be calculated as 5 mEq/cat every 24 hours (with additional potassium required if hypokalemia is present).

Diuretic therapy with furosemide (furosemide) can be added after rehydration and after any other electrolyte abnormalities are corrected. Diuretics are appropriate only if intravenous fluid therapy alone is not adequate to correct hypercalcemia. Bolus doses of 1 to 2 mg/kg can be used every 8 to 12 hours, or a constant-rate infusion of 2 to 6 mg/kg every 24 hours can be used. Care must be taken to ensure that the intravenous fluid

BOX 24-7

Acute Medical Management of Hypercalcemia

1. Identify and treat underlying cause.
2. Fluid therapy (0.9% saline) at 2-3 times maintenance rates.
 - Volume expansion to correct dehydration.
 - Diuresis increases renal calcium excretion.
 - Potassium supplementation usually required.
3. Diuretic therapy with furosemide (furosemide).
 - Use when fluids alone do not resolve hypercalcemia.
 - Ensure hydration-electrolyte balance has been corrected and is maintained.
 - Administer 1-2 mg/kg every 8-12 hours.
4. Calcitonin therapy
 - Use when fluid and diuretic therapy are not successful.
 - Administer 4-6 IU/kg subcutaneously every 8-12 hours.
 - May result in anorexia.
5. Bisphosphonates
 - There are few reports of use in cats.
 - Oral agents can result in esophagitis in humans.
6. Glucocorticoids
 - They should not be used until all diagnostic testing is complete.
 - They may decrease effectiveness of chemotherapy.

rates overcome the volume loss induced by diuretic therapy.

Calcitonin has not been frequently used in cats. It can be tried if fluid diuresis and diuretic treatment do not resolve hypercalcemia. Calcitonin is administered subcutaneously at 4 to 6 IU/kg every 8 to 12 hours. The magnitude and duration of effect are limited, although there is a fast onset of action. Calcitonin causes anorexia in dogs.⁸⁵

Intravenous bisphosphonates have been reported to reduce hypercalcemia in two cats (pamidronate disodium)⁴⁶ and have also been used for slowing of tumor growth and pathologic bone turnover associated with oral squamous cell carcinoma (zoledronate).¹⁰¹ Bisphosphonates reduce the activity and number of osteoclasts after binding to hydroxyapatite. Pamidronate was administered at 1.5 to 2 mg/kg given as a slow (approximately 4-hour) intravenous infusion diluted in normal saline; ionized calcium concentration returned to normal within 48 hours. One cat with idiopathic hypercalcemia remained normocalcemic for 9 weeks; the other cat had nodcardiosis, which was successfully treated, and no recurrence was reported.⁴⁶ Adequate hydration is required before bisphosphonates should be considered insofar as nephrotoxicity is a potential risk factor.

Glucocorticoids should not be administered to hypercalcemic cats until a diagnosis has been confirmed because they can interfere with the ability to reach a diagnosis, affect chemotherapy efficacy, and reduce immunity against infectious agents (that can cause hypercalcemia associated with granulomatous inflammation). The beneficial effects of glucocorticoids to manage hypercalcemia include reducing bone resorption of calcium, decreasing intestinal calcium absorption, and increasing renal calcium excretion; they are also cytotoxic to neoplastic lymphocytes (and therefore used as part of most chemotherapeutic protocols for these types of neoplasia). The previously noted therapies are rarely unsuccessful in managing hypercalcemia acutely. It is the author's opinion that glucocorticoids should be reserved to manage hypercalcemia in chronic cases when other therapy is unsuccessful.

Chronic Therapy

The key principle for chronic therapy of hypercalcemia is the same for acute management—that is, *manage the underlying cause*. In most cases, management of the underlying cause will be sufficient to reduce hypercalcemia. Consequently, the key condition for which chronic management must be instituted is when the diagnosis is idiopathic hypercalcemia—those instances when thorough investigation fails to uncover an underlying cause. The treatment options for chronic management of hypercalcemia are summarized in [Box 24-8](#).

BOX 24-8

Chronic Medical Management of Hypercalcemia

1. Identify and treat underlying cause.
2. Dietary therapy
 - High-fiber diets
 - Renal disease diets
 - Calcium oxalate–preventive diets
 - Canned diets
3. Subcutaneous fluids (0.9% saline)
 - Not assessed
 - Unlikely to be harmful
4. Low-dose diuretics such as frusemide (furosemide).
 - Not assessed in chronic situation
 - Potential for dehydration
 - Must evaluate for azotemia serially
5. Glucocorticoids
 - Should not be used until all diagnostic testing complete
 - Can decrease efficacy of chemotherapy
 - Prolonged use can increase risk of diabetes mellitus in susceptible cats
6. Bisphosphonates
 - Few reports in cats
 - Oral agents can result in esophagitis in humans

There have been mixed reports of the efficacy of dietary therapy in reducing hypercalcemia. One report noted a return to normocalcemia in all five cats fed a high-fiber diet.⁵⁸ In another study three cats were fed a high-fiber diet, three were fed an oxalate uolith-preventive diet, and three were fed a diet for management of CRD; there was minimal response to dietary therapy in any of these cats.⁶³ An oxalate uolith-preventive diet had no effect on ionized calcium concentrations in three cats with apparent idiopathic hypercalcemia in another study.⁵⁶

High-fiber diets may increase intestinal transit time of calcium; foods designed for cats with renal disease are lower in calcium and phosphorus; oxalate uolith-preventive diets are also calcium restricted; canned diets of any description are generally calcium restricted. There is no firm evidence for the benefits of dietary therapy, but insofar as this management is very unlikely to be harmful and many cats with idiopathic hypercalcemia do not show clinical signs for years, it is appropriate to try dietary therapy in the first instance.

The author recommends starting with canned high-fiber diets (e.g., Hill's Prescription Diet w/d Feline) or adding psyllium fiber (e.g., Metamucil, Procter & Gamble) to a maintenance canned diet and rechecking calcium values at 2- to 4-week intervals. If normocalcemia is not restored after 6 to 8 weeks, alternative diets can be tried similarly. Further therapy is warranted if no benefit is noted from any diet.

Subcutaneous fluid administration at home, as is often recommended for cats with renal insufficiency, is a potential management strategy for hypercalcemic cats. It is important to note that this treatment modality has not been critically assessed for this condition. However, there are few contraindications—namely, congestive heart failure, hypoalbuminemia, and edema or other evidence of fluid overload. Fluid overloading is difficult to achieve with subcutaneous therapy but is a potential issue in a cat with, for example, an unrecognized cardiomyopathy. Certainly, subcutaneous fluid administration is a sensible approach in a hypercalcemic cat that is azotemic because the treatment will, in most cases, manage the two conditions concurrently.

Diuretic therapy with low-dose frusemide (furosemide) has also not been critically assessed as management for chronic hypercalcemia. It is imperative to use extreme caution with diuretics in an already dehydrated (azotemic) cat, including cats with renal disease. Anecdotally, the author has found that cats vary immensely in their sensitivity to frusemide (furosemide). As little as 0.5 mg/kg (or 2.5 mg/cat) frusemide (furosemide) can reduce mild hypercalcemia in many cats and usually does not result in azotemia but can cause severe azotemia in some susceptible individuals. If a low dose is not effective in reducing hypercalcemia and is not causing azotemia, the dose can slowly be titrated upward with

weekly rechecks to assess calcium and azotemia. Other potential consequences of chronic diuretic administration are metabolic alkalosis with hypokalemia and reduction of sodium and chloride.

Glucocorticoids, in the form of prednisone (5 to 12.5 mg/cat daily) were effective in resolving hypercalcemia completely in four of six treated cats in one study.⁶³ Uncited textbook references note that 50% of cats respond to 5 to 10 mg/cat daily of prednisone or prednisolone, but some cats require up to 20 mg/cat daily to restore normocalcemia; some cats escape the effect of glucocorticoid treatment, and hypercalcemia can return despite maximal prednisone doses.^{23,85} Glucocorticoid therapy *must not* be initiated until neoplasia and granulomatous inflammation have been conclusively ruled out. In these circumstances, when other therapies have been unsuccessful, prednisone (or prednisolone) can be attempted at 5 mg/cat daily for 1 month before reassessment. If iCa remains increased, the dose can be titrated upward (with reassessments). Chronic administration of corticosteroids can induce DM in susceptible individuals (see *Endocrine Pancreatic Disorders*). Because of the concern that increased renal excretion of calcium induced by corticosteroids has the potential to aggravate hypercalciuria and calcium oxalate urolithiasis, appropriate monitoring should be instituted.⁶³

Bisphosphonates have not been thoroughly assessed but may become a routine alternative for management of hypercalcemia. Intravenous pamidronate was reported to result in normocalcemia for 9 weeks after a single dose of 1.5 to 2 mg/kg in one cat with idiopathic hypercalcemia.⁴⁶ The duration of effect is likely to vary from cat to cat and may vary with dose, but it is not unreasonable to suggest that intravenous pamidronate therapy approximately every 2 months may be appropriate management for a cat with idiopathic hypercalcemia. Further, an uncited textbook reference notes that a small number of cats have been treated successfully with 10 mg of alendronate orally once weekly for up to 1 year.²³ Erosive esophagitis is noted as a possibility in humans receiving bisphosphonates, but this risk is most associated with swallowing the medication with little or no water, lying down during or after ingestion of the tablet, continuing to take alendronate after the onset of symptoms, and having preexisting esophageal disorders.²⁷ These risks may be reduced in cats by following the medication with 5 mL of water syringed into the cat's mouth; dabbing butter on the cat's lips to promote licking and salivation has also been recommended.²³

HYPOCALCEMIA

Hypocalcemia is not a common clinical finding in cats. When present, signalment and history, with other clinical and routine laboratory findings, usually give

an indication of the underlying cause.⁷ For example, hypocalcemia in a queen in the first few weeks after delivery is most likely due to eclampsia; low calcium after thyroidectomy is most likely due to iatrogenic hypoparathyroidism; taking a thorough dietary history will help the clinician recognize nutritional secondary hyperparathyroidism. As with hypercalcemia, serum PTH and calcitriol concentrations can help confirm a diagnosis. Calcidiol and PTHrP concentrations are not usually helpful to distinguish causes of hypocalcemia.

Clinical Signs

The clinical signs due to hypocalcemia vary depending on the severity and rate of change of iCa concentrations; mild decreases in iCa concentration may not result in obvious clinical signs.⁷ Low plasma iCa increases the excitability of neuromuscular tissue. Typical signs seen are muscle tremors, stiff gait, and even generalized seizures; anorexia and lethargy are noted in cats with primary hypoparathyroidism. In severe cases circulatory effects (hypotension and decreased myocardial contractility) and paralysis of respiratory muscles can result in death.^{22,73}

Underlying Causes

Hypocalcemia develops when bone mobilization of calcium is reduced, skeletal calcium accretion is enhanced, urinary losses of calcium are increased, gastrointestinal absorption of calcium is reduced, calcium is translocated intracellularly, or a combination of these mechanisms occurs.⁸⁷ Common potential underlying causes of hypocalcemia, with associated biochemistry and calcemic hormone changes, are shown in **Table 24-17**. It should be noted that renal disease can cause hypocalcemia as well as hypercalcemia. Hypocalcemia has also been recognized in cats with acute pancreatitis and is associated with a poorer prognosis.⁵³

Primary Hypoparathyroidism

Primary hypoparathyroidism has been reported in the literature in cats on nine occasions. Aside from one small case series of five cats,⁷³ other descriptions have been single case reports.^{12,38,71,79} This appears to be a disorder of young cats with a mean reported age of 1.8 years (range 0.5 to 6.7 years), with four cats being 1 year old or less. Approximately equal numbers of male and female cases have been reported. All but two cats were domestic shorthairs (one Himalayan and one Siamese). Clinical signs were mostly those expected with prolonged hypocalcemia, such as seizures, tremors, and tetany. Cataracts were noted in five of the nine cases; bilateral protrusion of the nictitating membrane was noted in two cats.

TABLE 24-17 Anticipated Changes in Calcemic Hormones and Serum Biochemistry Associated with Common Disorders of Hypocalcemia

	tCa	iCa	Alb	PO ₄	PTH	PTHrP	25-OH vit D	1,25(OH) ₂ vit D
Hypoparathyroidism Idiopathic Iatrogenic	↓	↓	N	↑ or N	↓ or N	N	N	N or ↓
Secondary hyperparathyroidism Nutritional Renal	N or ↓	N or ↓	N	N or ↑	↑	N	↓ or N	N or ↓
Eclampsia	↓	↓	N	↓	Mild ↑ or N	N	N	N or ↓
Ethylene glycol toxicity	↓	↓	N	↑ or N	↑	N	N	↓ or N
Phosphate enema	↓	↓	N	↑	↑	N	N	Nor ↓ or ↑
Septic peritonitis	↓ or N	↓	↓ or N	N	↑ or N	N	N	N
Hypoalbuminemia	↓	N	↓	N	N or ↑	N	N	N or ↑

tCa, Total calcium; iCa, ionized calcium; Alb, albumin; PO₄, phosphate; PTH, parathyroid hormone; PTHrP, PTH-related peptide; 25-OH vit D, calcidiol; 1,25(OH)₂ vit D, calcitriol; N, normal.

Eight of nine hypocalcemic cats were also hyperphosphatemic (without azotemia). Some cats had elevated ALT values. PTH concentration was normal in the two cats in which it was measured. In physiologically normal cats, PTH should increase in the face of hypocalcemia. Histopathology of the parathyroid gland was assessed in three cases, and no parathyroid tissue was found in any. In one case a lymphocytic plasmacytic infiltrate was recognized adjacent to the cranial pole of a thyro-parathyroid lobe,³⁸ suggesting an immune-mediated mechanism.

Affected cats may initially require emergency therapy with intravenous calcium gluconate but subsequently require lifelong supplementation with oral calcium and calcitriol supplementation; phosphate binders have been used to reduce high phosphate concentrations. Approaches for therapeutic requirements are the same as for all causes of hypocalcemia and will be covered later in this chapter. When appropriate therapy is instituted, the prognosis is excellent.

Iatrogenic Hypoparathyroidism

Iatrogenic hypoparathyroidism can occur subsequent to parathyroidectomy (as discussed in the section on hyperparathyroidism), bilateral thyroidectomy, sudden correction of chronic hypercalcemia of malignancy, or alkali administration.

The sudden correction of chronic hypercalcemia can lead to hypocalcemia as a result of parathyroid gland atrophy and inadequate ability to synthesize and secrete PTH. This can be a consequence of surgical excision of the affected parathyroid gland on account of primary hyperparathyroidism caused by parathyroid gland adenoma. The degree of parathyroid gland atrophy depends on the magnitude of hypercalcemia and its duration before correction. Rapid correction of

hypercalcemia of malignancy after chemotherapy often results in mild hypocalcemia that is usually not associated with clinical signs, but clinical signs of hypocalcemia may occur in some cases.⁸⁷

Postoperative hypocalcemia is reported in 6% to 82% of cats undergoing bilateral thyroidectomy, depending on the surgical method.^{15,36} Hypoparathyroidism and associated hypocalcemia result from accidental removal of the external parathyroid glands or disruption of the vascular supply. This consequence becomes transient when parathyroid autotransplantation is used as outlined in the section on **Thyroid Gland Disorders**; in one study seven of eight cats regained normocalcemia within 20 days of bilateral thyroparathyroidectomy with parathyroid autotransplantation.⁷⁰ Hypocalcemia is a rare consequence of unilateral thyroidectomy.

The administration of alkaline agents may result in hypocalcemia. This has been recognized in a cat treated for salicylate intoxication with sodium bicarbonate.¹ Muscle fasciculations increased during treatment with sodium bicarbonate, and serum tCa was low. A single dose of intravenous sodium bicarbonate at 4 mEq/L to cats resulted in a maximal decrease of iCa 10 minutes after infusion; iCa remained below baseline for 3 hours.²⁰

Nutritional Secondary Hyperparathyroidism

Nutritional secondary hyperparathyroidism was once a common nutritional disease in small animals,¹³ being most frequently encountered in puppies and kittens fed exclusively all-meat diets.⁸⁹ More recent reports are sporadic,^{95,100} but two very recent papers^{30,64} demonstrate the continuing importance of this entity. Theoretically, nutritional secondary hyperparathyroidism may also occur when severe gastrointestinal disease is present (as has been reported in dogs and people), limiting the absorption of calcium and vitamin D.⁸⁷

The two major forms of clinical signs reflect either complications of severe osteopenia or typical signs of hypocalcemia. Typical radiographic findings include an extensive decrease in bone opacity (osteopenia) with decreased contrast between bones and soft tissue. Cortices are thin and diaphyseal, and metaphyseal trabeculation is coarse. Longitudinal limb growth and physeal appearance are normal. Pathologic fractures are a not-uncommon consequence. In contrast, the skull tends to be predominantly affected in osteodystrophy as a result of renal secondary hyperparathyroidism. Hypocalcemia signs can include muscle twitching, excitation, or generalized seizures.⁹⁵

The prognosis for uncomplicated cases is good, and dietary correction alone results in normalized mineralization in 4 to 8 weeks.^{30,95} Supplementing diets with additional calcium may accelerate osteoid mineralization but may represent a risk for hypercalcemia when calcitriol levels are markedly increased. Vitamin D administration may also be contraindicated because of its potentiating effect, in concert with PTH, on bone resorption.⁹⁵

Renal Secondary Hyperparathyroidism

The most likely causes of hypocalcemia in renal disease are decreased calcitriol synthesis by diseased kidneys and the response to markedly increased serum phosphorus concentration.⁸⁷ One study found that 15% of 74 cats with clinical renal disease were hypocalcemic on the basis of serum tCa.²⁹ Another found that hypocalcemia was underappreciated when based on results of only tCa measurement (and not iCa), especially with advancing azotemia. In that study 56% of 47 cats with advanced renal disease had ionized hypocalcemia. Only 14% of cats with moderate renal disease had ionized hypocalcemia, and no cats with "compensated" renal disease were hypocalcemic.⁸

Prevention of phosphate retention is central to the management of chronic renal disease, primarily using phosphate-restricted diets. Intestinal phosphate-binding agents can be used for additional phosphate restriction.⁷ Low-dose calcitriol therapy has been recommended but is clinically unproven.^{47,76}

Eclampsia

Puerperal tetany (eclampsia) is rare in cats but when present typically occurs between 1 and 3 weeks post partum and has been attributed to loss of calcium into milk during lactation.^{16,99} Eclampsia was described in four cats in which hypocalcemia developed 3 to 17 days *before* parturition. Signs of depression, weakness, tachypnea, and mild muscle tremors were most common; vomiting and anorexia were less common, and prolapse of the third eyelid occurred in some cats. Hypothermia, instead of hyperthermia as seen in dogs, was observed. All cats responded to parenteral calcium

gluconate initially and to oral calcium supplementation throughout gestation and lactation.³⁵ Calcium supplementation before parturition is not recommended for queens at risk of eclampsia because it may downregulate PTH secretion and actually increases the risk of eclampsia.⁹⁹

Toxic Exposures

PHOSPHATE ENEMAS

Phosphate enemas (e.g., Fleet enema, Johnson & Johnson) should not be used in cats because the rapid absorption of phosphate results in hyperphosphatemia that can be greater than five times the upper limit of normal. Such significant hyperphosphatemia results in hypocalcemia, with serum tCa decreasing within 45 minutes and persisting for 4 hours.^{4,49,96}

ETHYLENE GLYCOL

Ethylene glycol ingestion can result in hypocalcemia. This is due to chelation of calcium by a metabolite and calcium deposition in soft tissues. Hypocalcemia is recognized along with acute renal failure and hyperphosphatemia.⁹⁴

Septic Peritonitis

Hypocalcemia has been recognized with septic peritonitis in 59% of cats (20 of 34) in one study²⁵ and 89% of cats (49 of 55) in another.⁵² No specific signs of hypocalcemia were recognized in any cat in the latter study; although 10 cats in this study received calcium supplementation, no treatment benefit could be demonstrated. Treatment could potentially result in subclinical deleterious effects such as precipitation of calcium in soft tissues or excessive intracellular calcium accumulation, leading to cell death. Therefore routine treatment of hypocalcemia in the septic patient is not recommended. Failure of iCa concentration to normalize during hospitalization may be a negative prognostic indicator.⁵²

Hypoalbuminemia

Hypoalbuminemia may result in hypocalcemia because of a decrease in the protein-bound fraction of calcium. Ionized calcium should be evaluated in these circumstances but is usually normal, so clinical signs do not result. Correction formulae based on albumin concentration do not improve the prediction of actual iCa concentration and should not be used.⁸⁷

Treatment of Hypocalcemia

Treatment of hypocalcemia must take into account the underlying cause. Treatment of acute signs of hypocalcemia such as tetany or seizures is identical regardless of cause. However, some causes of hypocalcemia, such as nutritional secondary hyperparathyroidism,

eclampsia, and toxicities, will not require supplemental treatment beyond the acute phase. Conversely, conditions such as primary hypoparathyroidism and bilateral thyroparathyroidectomy (without parathyroid autotransplantation) will require lifelong treatment.

Hypocalcemia should be anticipated in cats that undergo bilateral thyroidectomy (even with parathyroid autotransplantation) because transiently lowered serum calcium concentrations can still occur. In humans, assessing PTH as well as calcium concentrations 24 hours after surgery has proved a useful predictor of postoperative hypoparathyroidism.³ Those cats undergoing parathyroidectomy for primary hyperparathyroidism should be monitored similarly to cats undergoing thyroidectomy. Preemptive therapy to increase serum calcium concentration is appropriate for cats with marked hypocalcemia that do not yet show clinical signs.

Acute Management of Tetany or Seizures

Tetany or seizures caused by hypocalcemia are an indication for an immediate infusion of intravenous calcium gluconate, administered to effect. Ten percent calcium gluconate at a dosage of 10 to 15 mg/kg (1 to 1.5 mL/kg) is slowly infused over a 10- to 20-minute period.^{22,74} Calcium gluconate is the calcium salt of choice because it is nonirritating if the solution is inadvertently injected perivascularly.²² Heart rate and, ideally, electrocardiogram should be monitored during this infusion; bradycardia and shortening of the Q-T interval are indicators of cardiotoxicity and, if recognized, the infusion should be slowed or temporarily discontinued.

Not all clinical signs abate immediately after acute correction of hypocalcemia; there may be a lag of 30 to 60 minutes before signs such as nervousness, panting, and behavioral changes abate, despite attainment of normocalcemia. This may reflect a lag in equilibration between cerebrospinal fluid and extracellular fluid calcium concentrations.²²

Subacute Management

The initial bolus injection of elemental calcium can be expected to decrease signs of hypocalcemia for as little as 1 hour to as long as 12 hours if the underlying cause of hypocalcemia is still present. Consequently, a constant-rate infusion of calcium gluconate administered with intravenous fluids is required at 60 to 90 mg/kg per day (2.5 to 3.75 mg/kg per hour) of elemental calcium until oral medications provide control of serum calcium concentration. Note that 10 mL of 10% calcium gluconate provides 93 mg of elemental calcium. For a 4-kg cat maintenance fluid rates are approximately 10 mL per hour, so approximately 2.5 mg/kg per hour (or 10 mg/4-kg cat per hour) of calcium is provided by adding 100 mL of calcium gluconate per 1 L fluids (as long as the fluid rate is maintained at 10 mL per hour). Calcium salts should not be added to fluids that contain lactate,

acetate, bicarbonate, or phosphates because calcium salt precipitates can occur.^{22,86}

Subcutaneous administration of calcium gluconate can result in iatrogenic calcinosis cutis, skin necrosis, and scarring at the injection site⁷⁹ and should be avoided. Oral calcium and calcitriol should be started as soon as possible while the cat is receiving intravenous calcium. The intravenous dose of calcium is reduced as oral calcium salts and calcitriol become effective at maintaining serum calcium.^{22,74,87}

Chronic Maintenance Therapy

Maintenance therapy is required for conditions (e.g., primary or iatrogenic hypoparathyroidism) for which parathyroid function is lost permanently so that PTH cannot be produced. PTH cannot be supplemented, although supplementing with calcitriol (the secretion of which is stimulated by PTH in a physiologically normal cat) suffices in most cases.

Initially, calcium also must be supplemented. However, in most patients a complete and balanced diet supplies a normal dietary intake of calcium and is sufficient to maintain adequate serum calcium concentrations *as long as calcitriol treatment is continued*. Consequently, oral calcium salt supplementation can be tapered and, for most cats, discontinued after calcitriol reaches adequate levels.^{7,87}

Calcium carbonate is the most widely used oral preparation of the calcium salts because it contains the greatest percentage of elemental calcium. Any given volume of calcium carbonate contains 40% of that volume of elemental calcium. Oral calcium is usually administered at 25 to 50 mg/kg per day by way of elemental calcium in divided doses (divided into three or four doses over a day). A 4-kg cat will require 100 to 200 mg daily of elemental calcium, which is equivalent to 250 to 500 mg daily of calcium carbonate. If serum phosphorus concentrations remain increased, oral calcium carbonate can be continued for its intestinal phosphate-binding effects.^{74,87}

Calcitriol is the vitamin D metabolite of choice to provide calcemic actions because it has the most rapid onset of maximal action and the shortest biologic half-life. The dose of calcitriol can be adjusted frequently because of its short half-life and rapid effects on serum calcium concentration. If hypercalcemia occurs, it abates quickly after dose reduction. A loading dose of 20 to 30 ng/kg daily has been recommended when more rapid correction of serum calcium concentration is desirable. A maintenance dose of 10 to 20 ng/kg daily divided and given twice daily ensures sustained priming effects on intestinal epithelium for calcium absorption.⁸⁷ Dose recommendations should be taken as guidelines, and individual doses should be determined for each cat on the basis of frequent evaluation of calcium concentrations.

Commercially available calcitriol capsules (Rocaltrol, Hoffman-LaRoche) of 0.25- and 0.50- μ g (250 and 500 ng) per capsule are not appropriate for cats because the doses are too high to be useful. Furthermore, it is difficult to divide capsules because active calcitriol within the capsule is in a liquid form. Fortunately, there is also a commercial liquid formulation of Rocaltrol with a concentration of 1 μ g/mL that can be used to dose cats appropriately. Compounding pharmacists are also able to make up appropriate doses of calcitriol for cats.

Periods of hypocalcemia and hypercalcemia occur sporadically in patients during initial efforts to manage serum calcium concentration. During the stabilization period, serum tCa should be assessed daily. Subsequently, until target serum calcium concentration has been achieved and maintained, serum calcium should be assessed weekly. Measurement of serum tCa concentration is recommended every 3 months thereafter in animals with permanent hypoparathyroidism. Serum calcium concentration should be adjusted to just below the normal reference range. This not only lessens the likelihood that hypercalcemia will develop but also reduces the magnitude of hypercalciuria that occurs in patients with PTH deficiency. Maintaining a mildly decreased serum calcium concentration also ensures a continued stimulus for hypertrophy of the remaining parathyroid tissue in patients with postoperative hypoparathyroidism.⁸⁷

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