

CHAPTER CONTENTS

Etiology, 348

Malignant Versus Benign Potential, 348

Pathophysiology, 349

Maintenance of Euglycemia in the Healthy Dog, 349

Hypoglycemia and the Counterregulatory Response, 350

Insulin Secretion in Dogs with Beta-Cell Neoplasia, 351

Mechanism for Insulin-Induced Hypoglycemia, 351

Origin of Clinical Signs, 351

Clinical Features, 352

Signalment, 352

History, 353

Physical Examination, 353

Clinical Pathologic Abnormalities, 354**Differential Diagnoses for Fasting Hypoglycemia, 355**

Congenital Hepatic Disease, 355

Acquired Hepatic Dysfunction, 355

Adrenocortical Insufficiency (Addison's Disease), 356

Glucagon Deficiency, 356

Hypopituitarism, 356

Non-Beta-Cell Tumors, 357

Neonatal and Juvenile Hypoglycemia, 357

Endotoxic or Sepsis-Induced Hypoglycemia, 358

Kidney Failure, 358

Polycythemia, 358

Artifactual Hypoglycemia, 358

Iatrogenic Hypoglycemia (Toxicities), 358

Diagnostic Approach to Hypoglycemia: Prioritizing the Differentials, 359**Confirming the Diagnosis of an Insulin-Secreting Beta-Cell Tumor: Serum Insulin Determination, 359**

Whipple's Triad, 359

Determination of Baseline Insulin and Glucose Concentrations, 360

Insulin-to-Glucose Ratios, 360

Serum Fructosamine Concentration, 361

Provocative Testing, 361

Diagnostic Imaging, 361

Radiography, 361

Ultrasonography, 361

Computed Tomography, 362

Scintigraphy, 363

Treatment of Beta-Cell Neoplasia, 364

Surgical Versus Medical Therapy, 364

Perioperative Management of Dogs Undergoing Surgery, 364

Medical Therapy for an Acute Hypoglycemic Crisis, 368

Medical Therapy for Chronic Hypoglycemia, 369

Prognosis, 372**Insulin-Secreting Beta-Cell Tumors**

in Cats, 372

Insulin-secreting beta-cell tumors (insulinomas) were first described in the dog by [Slye and Wells in 1935](#). During the past seven decades, numerous publications have appeared in the veterinary literature addressing the clinical manifestations, diagnosis, treatment, and pathology of beta-cell tumors in dogs. Insulin-secreting beta-cell neoplasia is an uncommon diagnosis in dogs and a rare entity in cats. Despite excellent documentation of this disease, increased awareness of the clinical presentations, and well-established methods for establishing the diagnosis, treatment options remain limited and the prognosis remains guarded to poor. This chapter summarizes current concepts regarding the diagnosis and treatment of insulin-secreting beta-cell tumors in dogs and cats.

**ETIOLOGY**

Functional tumors arising from the beta cells of the pancreatic islets are malignant tumors that secrete insulin independent of the typically suppressive effects of hypoglycemia. Insulin is the most common product demonstrated in the neoplastic cells, and the clinical signs in such animals are primarily those that result from insulin-induced hypoglycemia. Beta-cell tumors, however, are not completely autonomous, and they respond to provocative stimuli, such as an increase in blood glucose by secreting insulin, often in excessive amounts. Immunohistochemical analysis of

beta-cell tumors has revealed a high incidence of multihormonal production, including pancreatic polypeptide, somatostatin, glucagon, serotonin, and gastrin ([Hawkins et al, 1987](#); [O'Brien et al, 1987](#); [Minkus et al, 1997](#)). Recently, using quantitative real-time polymerase chain reaction (PCR), significantly higher expression of genes encoding for growth hormone (GH) and insulin-like growth factor-1 (IGF-1) have been identified in metastases, compared to the primary beta-cell tumor and immunohistochemical examination of the beta-cell tumor and its metastases revealed expression of GH, IGF-1, and GH receptor in both primary beta-cell tumors and metastases ([Buishand et al, 2012](#)). The authors speculated that therapeutic intervention with agents that specifically antagonize the GH/IGF-1 axis or members of their signaling cascade may inhibit beta-cell tumor growth.

Malignant Versus Benign Potential

Beta-cell tumors are notorious for masking their malignant tendencies in the dog. Discrepancy is noted between the orderly arrangement of well-differentiated cells, the rarity of mitotic figures in most islet cell tumors, and the frequent metastasis of beta-cell tumors at the time of diagnosis ([Kruth et al, 1982](#)). Classifying beta-cell tumors as adenomas or adenocarcinomas based on their morphology often does not reflect their biologic behavior

in humans and dogs (Mehlhoff, et al, 1985; Minkus et al, 1997). Differentiation of malignant from benign neoplasia is usually based on identification of metastasis at surgery or necropsy or the recurrence of hyperinsulinism and hypoglycemia days to months after surgical removal of a “solitary” pancreatic mass. Recent histopathologic evaluation of beta-cell tumors in 26 dogs revealed that 96% were highly cellular and exhibited nuclear atypia and 83% had an infiltrative growth pattern (Buishand et al, 2010). Vascular invasion was common, but the mitotic index was low in most tumors. Increased stromal fibrosis within the tumor was the only significant morphological prognostic marker identified in the study, a finding that illustrates the general lack of prognostic significance of histopathologic criteria in beta-cell tumors (Kruth et al, 1982; Mehlhoff et al, 1985; Caywood et al, 1988).

The malignant potential of beta-cell tumors is often underestimated in the dog. In our experience, virtually all beta-cell tumors in dogs are malignant, and most animals have microscopic or grossly visible metastatic lesions at the time of surgery. The most common sites of tumor spread are the regional lymphatics and lymph nodes (duodenal, mesenteric, hepatic, splenic), the liver, and the peripancreatic omentum. Pulmonary metastasis is typically not recognized until very late in the disease process. Identification of distant metastasis such as the gastrointestinal tract or bone marrow or gross invasion of the tumor into major blood vessels with tumor thrombus formation is uncommon (Pickens et al, 2005; Hambrook and Kudnig, 2012). In most dogs, hypoglycemia recurs days to weeks after surgical excision of the tumor. The high incidence of metastasis at the time afflicted dogs are initially examined results in part from the typically protracted time for worrisome clinical signs (e.g., collapsing episodes, seizures) to develop and become apparent to the owner and the interval between the time an owner initially observes signs and when assistance is sought from a veterinarian. Most dogs are symptomatic for 1 to 3 months before being brought to a veterinarian.



PATHOPHYSIOLOGY

Maintenance of Euglycemia in the Healthy Dog

Glucose is essentially the sole metabolic fuel for the brain under normal physiologic conditions. Survival of the brain requires a continuous supply of glucose from the circulation which, in turn, requires maintenance of blood glucose concentration within or above the physiologic range. Glucose is derived from three sources: intestinal absorption that occurs after digestion of dietary carbohydrates; glycogenolysis, which is the breakdown of glycogen; and gluconeogenesis, which is the formation of glucose from precursors including lactate, amino acids (especially alanine and glutamine), and glycerol (Cryer, 2011). The liver is the major source of net endogenous glucose production through glycogenolysis and gluconeogenesis.

Exogenously derived energy, in the form of ingested carbohydrate, fat, and protein, provides enough fuel for 4 to 8 hours of cell metabolism. After this postprandial period, fuel for cellular metabolism must be derived from endogenous sources, primarily through production of glucose by the liver (Fig. 9-1). The liver initially provides glucose by the breakdown of stored hepatic glycogen (glycogenolysis). Liver glycogen stores are exhausted slowly in dogs, requiring 2 to 3 days of fasting, compared with only 24 hours of fasting in humans (de Bruijne et al, 1981). Hepatic glucose production is augmented by gluconeogenesis as the postprandial period increases and hepatic glycogen stores become depleted (Rothman et al, 1991). Gluconeogenesis is the formation of glucose from precursors (e.g., alanine, glutamine, lactate,

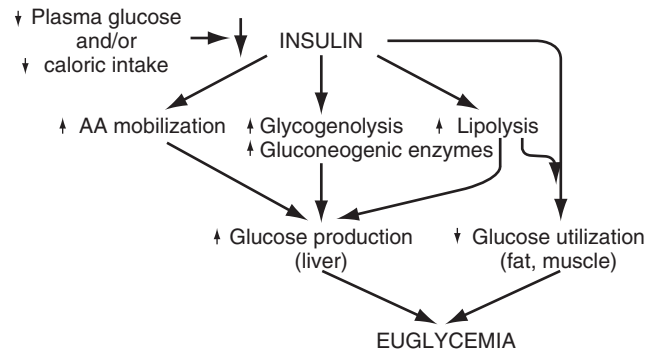


FIGURE 9-1 Hormonal and substrate changes by which euglycemia is maintained (and hypoglycemia is prevented) in normal subjects during a fast. The fall in the plasma insulin concentration is the key hormonal change resulting in increased glucose production and decreased glucose utilization. The decline in the plasma insulin concentration is, in turn, a result of a small decrease in the plasma glucose level (5 to 10 mg/dL) and/or a decrease in caloric intake. AA, Amino acid.

glycerol) delivered to the liver from peripheral stores. Muscle and other structural tissues supply amino acids, mainly alanine; blood cell elements supply lactate, the end product of glycolytic metabolism; and adipose tissue supplies glycerol from lipolysis of triglycerides (Karam, 2001). Oxidation of free fatty acids released from adipose cells during lipolysis supplies the energy required for gluconeogenesis and provides ketone bodies (i.e., acetoacetate, β -hydroxybutyrate), which can serve as alternative metabolic fuels for the brain during periods of prolonged fasting. Other requirements include a normal hepatic circulation, functioning hepatocytes capable of removing substrates from the circulation, and a complete complement of hepatic enzymes capable of converting these noncarbohydrate precursors into glucose.

The renal cortex also has the requisite enzymes for the production and release of glucose into the circulation, albeit the contribution is only about 5% during fasting (Stumvoll et al, 1995; Gerich et al, 2001). However, renal glucose production is regulated and under certain circumstances (e.g., glucose counterregulation, hepatic insufficiency) the contribution of glucose derived from renal gluconeogenesis can be as high as 40%. The kidney does not have glycogen stores and depends on gluconeogenesis as its only source of glucose production. Glutamine rather than alanine is the predominant amino acid substrate for renal gluconeogenesis. In addition to its contribution to glucose homeostasis during fasting, the kidney has been shown to be an important contributor to increasing blood glucose (i.e., glucose counterregulation) in the event of hypoglycemia. Although glucagon does not affect the kidney, the counterregulatory increase in epinephrine has been shown to stimulate gluconeogenesis in the renal cortex (Stumvoll et al, 1995; Gerich et al, 2001).

A normally functioning endocrine system is also necessary to maintain glucose homeostasis and prevent hypoglycemia. Rates of endogenous glucose influx into the circulation and glucose efflux out of the circulation into tissues other than the brain are regulated primarily by the blood glucose-lowering hormone insulin and the blood glucose-raising hormones, glucagon and epinephrine, such that systemic glucose balance is maintained, hypoglycemia and hyperglycemia are prevented, and a continuous supply of glucose to the brain is ensured (Cryer, 2011). In humans, when the blood glucose concentration exceeds approximately 110 mg/dL (6.2 mmol/L), insulin is secreted and the blood glucose concentration declines into the normal physiologic range (i.e., 70 to 110 mg/dL;

BOX 9-1 Autonomic Nervous System Response to Hypoglycemia**Alpha-Adrenergic Effects**

Inhibition of endogenous insulin secretion
Stimulation of peripheral vasoconstriction causing increase in cerebral blood flow

Beta-Adrenergic Effects

Stimulation of hepatic and muscle glycogenolysis
Stimulation of plasma glucagon secretion
Stimulation of lipolysis generating free fatty acids
Impairment of glucose uptake by muscle
Increase in cardiac output causing increase in cerebral blood flow

Adrenomedullary Catecholamine Effects

Augmentation of alpha- and beta-adrenergic effects

Cholinergic Effects

Stimulation of pancreatic polypeptide secretion
Increase gastric motility
Produce hunger

Adapted from Karam JH: Hypoglycemic disorders. In Gardner DA, Shoback D, editors: *Greenspan's basic & clinical endocrinology*, ed 9, New York, 2011, McGraw-Hill, with permission.

3.9 to 6.2 mmol/L). When the blood glucose concentration decreases toward the lower limit of the normal physiologic range, insulin synthesis and secretion is inhibited, which limits tissue utilization of glucose and allows the blood glucose concentration to increase. If the blood glucose concentration decreases below the normal reference range, increased secretion of glucose counterregulatory hormones, most notably glucagon and epinephrine, increase the blood glucose concentration back into the normal physiologic range.

The signaling pathways in the pancreatic beta cell provide the mechanism whereby insulin secretion rates respond to changes in blood glucose concentration. Glucose enters the beta cell by facilitated diffusion mediated by glucose transporter 2 (GLUT-2) (see Origin of Clinical Signs). Intracellular glucose is phosphorylated to glucose-6-phosphate by the enzyme glucokinase. Evidence suggests that glucokinase, by determining the rate of glycolysis, functions as the glucose sensor of the beta cell and is the primary mechanism by which the rate of insulin secretion adapts to changes in blood glucose (Buse et al, 2011). An increase in blood glucose levels results in an increase in the rate of glycolysis and a corresponding increase in the rate of insulin secretion by the beta cell, and vice versa. See the Insulin Synthesis, Structure, and Regulation section in Chapter 7 for more information on this topic.

Hypoglycemia and the Counterregulatory Response

The brain is wholly dependent on plasma glucose and counteracts declining plasma glucose concentrations with a carefully programmed neurogenic and hormonal response to mobilize storage depots of glycogen and fat and raise the plasma glucose concentration (Boxes 9-1 and 9-2). Hepatic glycogen reserves and gluconeogenesis in the liver and kidney directly supply the brain with glucose, and the mobilization of fatty acids from triglyceride depots provides energy for the large mass of skeletal and cardiac muscle, the renal cortex, the liver, and other tissues that use fatty acids as basic fuel; this spares glucose for use by tissues that remain dependent on glucose, including the central nervous system (CNS), erythrocytes, bone marrow, and renal medulla (Karam, 2001). The cascade of

BOX 9-2 Insulin and Counterregulatory Hormonal Response to Hypoglycemia**Insulin: Decreased Secretion**

Reduced stimulation of beta cells by low glucose
Inhibition of insulin secretion by alpha-adrenergic nervous system and adrenomedullary catecholamines
Primary glucose regulatory factor, first defense against hypoglycemia

Glucagon: Increased Secretion

Direct stimulation of alpha cells by low glucose
Stimulation of glucagon secretion by beta-adrenergic nervous system and adrenomedullary catecholamines
Primary glucose counterregulatory factor, second defense against hypoglycemia

Catecholamines: Increased Secretion

Direct stimulation of sympathetic nervous system by low glucose
Direct secretion from the adrenal medulla in response to low glucose
Involved, third defense against hypoglycemia

Adrenocorticotropic Hormone and Cortisol: Increased Secretion

Direct stimulation of pituitary adrenocorticotropic hormone (ACTH) secretion in response to low glucose
Stimulation of pituitary-adrenocortical axis by the sympathetic nervous system
Involved but not critical

Growth Hormone: Increased Secretion

Direct stimulation of growth hormone (GH) in response to low glucose
Involved but not critical

events leading to endogenous glucose production is initiated by a blood glucose concentration that decreases below the normal physiologic range and the hormonal and neurogenic response to hypoglycemia intensifies as the hypoglycemia becomes more severe.

Insulin is the dominant glucose-lowering hormone. Hypoglycemia suppresses insulin secretion, which facilitates the mobilization of energy from existing energy stores (glycogenolysis, lipolysis), promotes hepatic gluconeogenesis and ketogenesis, promotes renal gluconeogenesis, and decreases glucose utilization by insulin-dependent tissues (Cryer and Polonsky, 1998; Karam, 2001). Glucose-raising or counterregulatory hormones include glucagon, epinephrine, GH, and cortisol (see Box 9-2). Insulin-induced hypoglycemia causes an increase in plasma glucagon, epinephrine, and norepinephrine concentrations at the onset of the glucose counterregulatory response, with increases in plasma GH and cortisol occurring later. Glucagon is the key counterregulatory hormone affecting recovery from acute hypoglycemia. In response to falling plasma glucose levels, glucagon is secreted by the alpha cells of the pancreatic islets into the hepatic portal circulation; it acts exclusively on the liver to activate glycogenolysis and gluconeogenesis (Cryer, 2011). Hepatic glucose production increases almost immediately.

The adrenergic-catecholamine response to hypoglycemia also plays a major role in recovery from hypoglycemia. Epinephrine has both direct and indirect effects, which stimulate hepatic glycogenolysis and hepatic and renal gluconeogenesis; provide muscle tissue with an alternative source of fuel by mobilizing muscle glycogen and stimulating lipolysis; mobilize gluconeogenic precursors (e.g., lactate, alanine, and glycerol); and inhibit glucose utilization by insulin-sensitive tissues (e.g., skeletal muscle) (Cryer, 1993; Karam, 2001). The role of cortisol and GH in the acute response to hypoglycemia is minimal but cortisol and GH may play roles in the

defense against prolonged hypoglycemia (Boyle and Cryer, 1991). Cortisol facilitates lipolysis, promotes protein catabolism and the conversion of amino acids to glucose by the liver and kidney, and limits glucose utilization by insulin-dependent tissues. Similarly, GH promotes lipolysis and antagonizes the action of insulin on glucose utilization in muscle cells. However, the hyperglycemic effects of cortisol and GH do not appear for several hours after the hypoglycemic episode (Cryer and Polonsky, 1998).

The adrenergic neurogenic response to hypoglycemia acts directly to raise the blood glucose concentration and to stimulate hormonal responses that augment the adrenergic mobilization of energy stores (see Box 9-1). In dogs, hepatic glucose autoregulation is also an important glucose counterregulatory factor (Cryer and Polonsky, 1998). That is, the rate of hepatic glucose production is an inverse function of the blood glucose concentration independent of hormonal and neural regulatory factors.

Insulin Secretion in Dogs with Beta-Cell Neoplasia

In the dog or cat with an insulin-secreting tumor, neoplastic beta cells autonomously synthesize and release insulin despite hypoglycemia. As a result, tissue utilization of glucose continues, hypoglycemia progressively worsens, and clinical signs eventually appear. The onset of clinical signs is related to both the degree of hypoglycemia achieved and the rate at which it occurs. For example, a blood glucose concentration that gradually drops to 35 mg/dL (2 mmol/L) over an extended period (i.e., weeks) is much less likely to result in signs of hypoglycemia than is a blood glucose concentration of 35 mg/dL that develops rapidly over a few hours.

Failure of insulin secretion to decrease during periods of hypoglycemia predisposes a dog or cat with a beta-cell tumor to develop clinical signs of hypoglycemia during fasting and exercise. Insulin-secreting beta-cell tumors also remain responsive to many of the stimuli that promote insulin secretion in the healthy dog or cat, but the secretory response is often exaggerated, resulting in severe hypoglycemia. For example, clinical signs of hypoglycemia may occur after consumption of food that is easily digestible and rapidly absorbed or rapid intravenous (IV) administration of glucose to correct hypoglycemia.

Mechanism for Insulin-Induced Hypoglycemia

Insulin-secreting tumors and the associated hyperinsulinemia interfere with glucose homeostasis by decreasing the rate of glucose release from the liver and increasing the utilization of glucose by insulin-sensitive tissues (e.g., muscle, adipose tissue). Insulin interferes with mechanisms that promote hepatic glucose output by limiting circulating concentrations of substrates needed for gluconeogenesis. This effect is accomplished by inhibiting enzymes necessary for mobilizing amino acids from muscle and glycerol from adipose tissue. In addition, insulin decreases the activity of hepatic enzymes used in gluconeogenesis and glycogenolysis. Insulin also lowers blood glucose concentrations by stimulating glucose uptake and utilization in the liver, muscle, and adipose tissue. In essence, insulin increases tissue utilization of glucose already present in the extracellular space while interfering with hepatic production of glucose. The net effect is decreasing blood glucose concentrations because of increased tissue utilization of glucose.

Origin of Clinical Signs

Glucose is the primary fuel used by the CNS. Carbohydrate reserves in neural tissue are limited, and function of these cells

depends on a continuous supply of glucose from sources outside the CNS. If the blood glucose concentration drops below a critical level, nervous system dysfunction occurs. In mammals the cerebral cortex is the first area to be affected by a shortage of glucose. The metabolically slower vegetative centers in the brainstem have less demand for blood glucose and are affected after the cerebral cortex.

The entrance of glucose into the neurons of the CNS occurs primarily by diffusion and is not insulin dependent. Because cell membranes are impermeable to hydrophilic molecules (e.g., glucose), all cells require carrier proteins to transport glucose across the lipid bilayers into the cytosol. All cells except those in the intestine and kidney have non-energy-dependent transporters that facilitate diffusion of glucose across cell membranes. To date, fourteen facilitative transporters have been identified in humans, and they include transporters for substrates other than glucose, including fructose, myoinositol, and urate (Thorens and Mueckler, 2010). The primary transporters involved in facilitative diffusion of glucose into cells are called *GLUT-1* through *GLUT-4*, with the numbers designating the order of their identity (Table 9-1). GLUT-1 is present in all tissues, has a very high affinity for glucose, and appears to mediate basal glucose uptake. GLUT-1 is an important component of the brain vascular system (blood brain barrier) that ensures adequate transport of plasma glucose into the CNS (Fig. 9-2). GLUT-2 has very high expression in pancreatic beta cells and the basolateral membranes of intestinal and renal epithelial cells and hepatocytes. GLUT-3 is the major glucose transporter on the neuronal surface, has a very high affinity for glucose, and is responsible for transferring glucose from the cerebrospinal fluid (CSF) into the neuronal cells. GLUT-4 is the major glucose transporter in adipocytes and skeletal muscle.

Blood insulin concentrations do not affect neuronal glucose transport or utilization. However, if hyperinsulinemia results in an inadequate glucose supply for intracellular oxidative processes in neurons, a resultant decline occurs in energy-rich phosphorylated compounds (adenosine triphosphate [ATP]) in neurons. This in turn results in cellular changes typical of hypoxia, increased vascular permeability, vasospasm, vascular dilation, and edema. Neuron death from anoxia follows. In acute hypoglycemia, histologic alterations are most marked in the cerebral cortex, basal ganglia, hippocampus, and vasomotor centers (see Feldman and Nelson [1987] for references). Although most of the damage from hypoglycemia occurs in the brain, peripheral nerve degeneration and

TABLE 9-1 GLUCOSE TRANSPORTERS IDENTIFIED IN HUMANS

NAME	MAJOR SITES OF EXPRESSION	AFFINITY FOR GLUCOSE*
GLUT-1	Brain vasculature, red blood cells, all tissues	High ($K_m = 1$ mmol/L)
GLUT-2	Liver, pancreatic B cells, serosal surfaces of gut and kidney	Low ($K_m = 15$ -20 mmol/L)
GLUT-3	Brain neurons, also found in all tissues	High ($K_m < 1$ mmol/L)
GLUT-4	Muscle, fat cells	Medium ($K_m = 2.5$ to 5 mmol/L)

From Masharani U, Karam JH: Pancreatic hormones and diabetes mellitus. In Greenspan FS, Gardner DG, editors: *Basic and clinical endocrinology*, ed 6, New York, 2001, Lange Medical Books/McGraw-Hill, p. 630.

GLUT, Glucose transporter.

* K_m represents the level of blood glucose at which the transporter has reached one-half of its maximum capacity to transport glucose. It is inversely proportional to the affinity.

demyelination are sometimes encountered (Braund et al, 1987). Other major organ systems, such as the heart, kidneys, and liver, also depend on glucose. However, an acute decrease in the blood glucose concentration results in clinical signs that involve the CNS before signs of any other major organ system dysfunction become apparent.

Prolonged, severe hypoglycemia may result in irreversible brain damage; however, it is uncommon for a dog to die during a hypoglycemic episode. Hypoglycemia is a potent stimulus for the release of the counterregulatory hormones that function to antagonize the effects of insulin and stimulate an increase in the blood glucose concentration (see Hypoglycemia and the Counterregulatory Response).

The clinical manifestations of hypoglycemia are believed to result from both a lack of glucose supply to the brain (neuroglycopenia) and stimulation of the sympathoadrenal system. The

neuroglycopenic signs common to dogs include lethargy, weakness, ataxia, disorientation, abnormal behavior, and seizures (Table 9-2). Clinical signs resulting from stimulation of the sympathoadrenal system include muscle tremors, shaking, nervousness, and restlessness. In humans, the symptoms related to release of catecholamines often precede those of neuroglycopenia and act as an early warning sign of an impending hypoglycemic attack (Karam, 2001). This illustrates the rapid response of catecholamine secretion to hypoglycemia and partly explains why canine patients with insulin-secreting tumors do not always progress to generalized seizure activity during a fast.

CLINICAL FEATURES

Signalment

Insulin-secreting tumors typically occur in middle-aged or older dogs. The mean age at the time of diagnosis of an insulin-secreting tumor in 123 dogs in our series at University of California, Davis (UC Davis), was 9 years, with a median age of 10 years and an age range of 3 to 14 years (Fig. 9-3). There is no gender predilection. A variety of breeds have been diagnosed with an insulin-secreting tumor at our hospital (Table 9-3). Labrador Retrievers and Golden Retrievers are the breeds most commonly diagnosed with this disease, which is probably a reflection of breed popularity in our region rather than a breed predisposition per se. In general, insulin-secreting

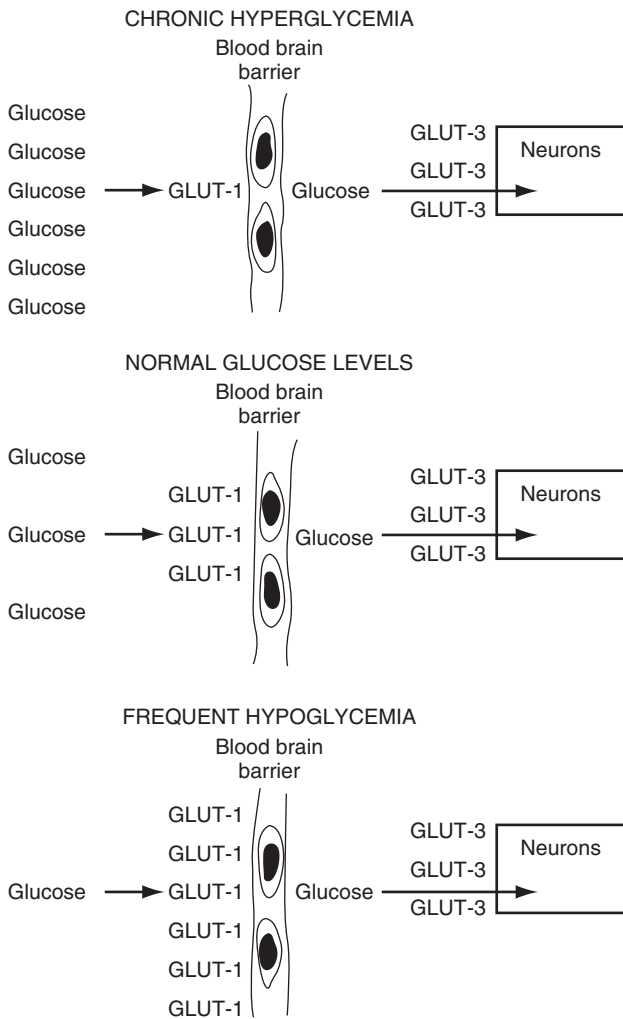


FIGURE 9-2 Glycemic regulation of glucose transporters. The center panel depicts the normal component of the high-affinity glucose transporter 1 (GLUT-1) on the vascular cells of the central nervous system (CNS) during euglycemia. An appropriate amount of glucose diffuses across the blood brain barrier and is transported into the neurons by another high-affinity glucose transporter, GLUT-3. The upper and lower panels, respectively, show adaptation by either downregulation of GLUT-1 in the face of chronic hyperglycemia (upper panel) or upregulation of GLUT-1 in the presence of chronic hypoglycemia. (From Karam JH: Hypoglycemic disorders. In Greenspan FS, Gardner DG, editors: *Basic and clinical endocrinology*, ed 6, New York, 2001, Lange Medical Books/McGraw-Hill, p. 701.)

TABLE 9-2 CLINICAL SIGNS ASSOCIATED WITH INSULIN-SECRETING TUMORS IN 117 DOGS

CLINICAL SIGN	NUMBER OF DOGS	PERCENT AGE
Weakness	73	62
Seizures	61	52
Collapse	38	32
Tremors, shaking	25	21
Ataxia	22	19
Disoriented, abnormal behavior	22	19
Lethargy	21	15
Polyphagia	6	5
Weight gain	6	5

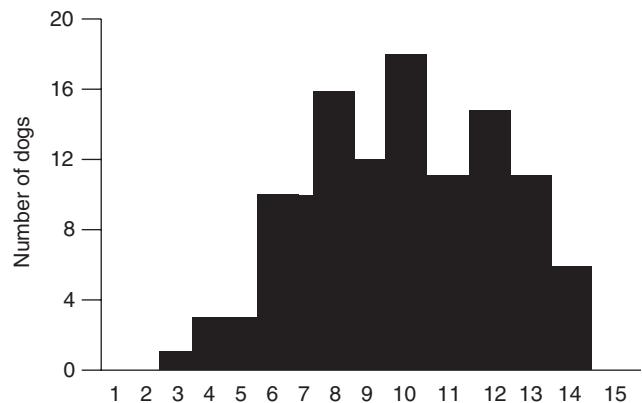


FIGURE 9-3 Age of 123 dogs at the time of initial diagnosis of an insulin-secreting islet cell tumor.

TABLE 9-3 BREED DISTRIBUTION OF 115 DOGS WITH ISLET CELL TUMORS

BREED	NUMBER OF DOGS	PERCENT
Labrador Retriever	17	15
Golden Retriever	11	10
Mixed-breeds	9	8
German Shepherd dog	7	6
Boxer	7	6
Terriers (Fox, Kerry Blue, West Highland White, Norwich)	7	6
Poodle	6	5
Irish Setter	6	5
Cocker Spaniel	6	5
Collie	5	4
Rottweiler	5	4
Border Collie	4	3
Doberman Pinscher	3	3
Samoyed	2	2
Staffordshire Terrier	2	2
Dachshund	2	2
Other breeds (one dog each)	16	10

tumors occur more commonly in large breeds of dogs. However, the size of the dog should never preclude an investigation for an insulin-secreting tumor in a hypoglycemic dog. We have diagnosed insulin-secreting tumors in dogs as small as a Pomeranian.

History

Clinical signs of an insulin-secreting tumor may have been observed for more than a year or as briefly as 1 day before veterinary care is sought. Most dogs, however, are symptomatic for 1 to 3 months before being brought to a veterinarian. In our most recent 30 dogs with an insulin-secreting tumor, clinical signs had been observed by the owners for an average of 5 weeks (range, 2 days to 4 months) before veterinary care was sought.

Clinical signs of an insulin-secreting tumor typically are caused by hypoglycemia and an increase in circulating catecholamine concentrations and include weakness, seizures, collapsing episodes, tremors, ataxia, and disorientation (see Table 9-2). One characteristic of hypoglycemic signs, regardless of the cause, is their episodic nature. Signs are generally observed intermittently for only a few seconds to minutes because of the compensatory counterregulatory mechanisms that usually increase the blood glucose concentration after the development of hypoglycemia. If these mechanisms are inadequate, seizures may occur as the blood glucose concentration continues to decrease. Seizures are usually self-limiting, typically lasting from 30 seconds to a few minutes. The seizure may stimulate further catecholamine secretion and activation of other counterregulatory mechanisms that increase the blood glucose concentration above critical levels (see Hypoglycemia and Counterregulatory Response).

The severity of clinical signs depends on the duration and severity of the hypoglycemia. Dogs with chronic fasting hypoglycemia or with recurring episodes appear to tolerate low blood glucose

concentrations (i.e., 20 to 30 mg/dL; 1.1 to 1.7 mmol/L) for prolonged periods without clinical signs, and only small additional changes in the blood glucose concentration are then required to produce symptomatic episodes. In these dogs, fasting, excitement, exercise, and eating may trigger the development of clinical signs. The “adaptation process” to chronic severe hypoglycemia is believed to involve “up-regulation” of the high-affinity glucose transporter, GLUT-1, on the vascular cells forming the blood brain barrier (see Fig. 9-2) (Karam, 2001).

In the healthy, exercising dog, a balance between increased glucose utilization by muscle, decreased glucose utilization by other tissues, and increased glucose production by the liver maintains the circulating blood glucose concentration in the normal range, allowing the brain to continue to function. The exercising dog with an insulin-secreting tumor has continuing glucose utilization not just by muscle but by all tissues, owing to the autonomous and continuing secretion of insulin. In addition, hepatic release of glucose is impaired. The potential for severe hypoglycemia is great, and this fact is supported by the number of owners who associate symptoms in their pets with jogging, play, or long walks. A similar pathophysiology is thought to explain the development of symptoms during periods of excitement. Insulin-secreting tumors are responsive to increases in the blood glucose concentration, and the insulin-secretory response can be exaggerated if the dog consumes food that is easily digestible and rapidly absorbed.

Physical Examination

Physical examination findings in dogs with an insulin-secreting tumor are often surprisingly unremarkable; dogs are usually free of visible or palpable abnormalities. Most abnormalities identified on the physical examination are nonspecific (Table 9-4). Weakness and lethargy, the most common findings, are identified in 29% and 17% of our cases, respectively. Episodes of collapse and seizures may occur during the examination but are uncommon. Afflicted dogs are usually free of palpable abnormalities, aside from findings commonly associated with aging. Weight gain is evident in some dogs and is a result of the anabolic effects of excess insulin in a dog with a normal or increased appetite. Failure to identify abnormalities on the physical examination, especially in an older, large-breed dog, is an important finding supportive of an insulin-secreting tumor.

Peripheral Neuropathy

Peripheral neuropathies have been reported in dogs with insulin-secreting tumors (Shahar et al, 1985; Braund et al, 1987; Van Ham et al, 1997). Clinical signs and physical examination findings range from paraparesis to tetraparesis, facial paresis to paralysis, sciatic hyporeflexia to areflexia, hypotonia, and muscle atrophy of the appendicular, masticatory and/or facial muscles. Sensory nerves may also be affected. A subclinical polyneuropathy has also been reported (Braund et al, 1987). The onset of clinical signs may be acute (days) or insidious (weeks to months). Abnormalities identified on electrodiagnostic testing include abnormal spontaneous potentials (e.g., positive sharp waves, fibrillation potentials) and slowed motor nerve conduction velocities (Braund et al, 1987). CSF analysis is usually unremarkable (Van Ham et al, 1997). Histopathologic findings in motor and sensory nerves include moderate to severe axonal necrosis, nerve fiber loss, and variable demyelination-remyelination (Braund et al, 1987; Schrauwen et al, 1996; Van Ham et al, 1997). Muscle changes reflect neurogenic atrophy. The pathogenesis of the polyneuropathy is not known. Proposed theories include metabolic derangements of the nerves induced by chronic and severe hypoglycemia or some

TABLE 9-4 PHYSICAL EXAMINATION FINDINGS ASSOCIATED WITH INSULIN-SECRETING TUMORS IN 78 DOGS

PHYSICAL EXAMINATION FINDING	NUMBER OF DOGS	PERCENTAGE
Weakness	23	29
Lethargy	13	17
Collapsing	6	8
Tremors	5	6
Obtunded	5	6
Peripheral neuropathy	5	6
Seizures	4	5
No abnormalities identified	43	55

other tumor-induced metabolic deficiency, an immune-mediated paraneoplastic syndrome resulting from shared antigens between tumor and nerves, or toxic factors produced by the tumor that deleteriously affect the nerves (Kudo and Noguchi, 1985; Das and Hochberg, 1999; Heckmann et al, 2000). Treatment is aimed at surgical removal of the beta-cell tumor (Jeffery et al, 1994). Prednisone therapy (initially 0.5 mg/kg every 12 hours) may improve clinical signs (Van Ham et al, 1997). Correction of hypoglycemia, by itself, may or may not improve clinical signs caused by the peripheral neuropathy (Bergman et al, 1994). In our experience, the prognosis for improvement in clinical signs is guarded to poor, although the occasional dog shows remarkable improvement in ambulation following removal of the tumor and reestablishment of a normal blood glucose concentration.

CLINICAL PATHOLOGIC ABNORMALITIES

Virtually all dogs with insulin-secreting tumors remain undiagnosed and often unsuspected of having such tumors after completion of the history and physical examination. Most afflicted dogs have a history of episodic weakness or seizures—signs that encompass a wide variety of disorders (Box 9-3). The minimum diagnostic evaluation for dogs with these clinical signs should include a complete blood count (CBC), serum biochemical panel, and urinalysis in an effort to identify abnormalities supportive of one of the disorders outlined in Table 9-3. Therapy other than that required in an emergency situation should be withheld until a diagnosis has been made.

Results of the CBC and urinalysis in dogs with an insulin-secreting tumor are usually normal. Results of the serum biochemical profile, aside from the blood glucose concentration, are also usually normal. Hypoalbuminemia, hypophosphatemia, hypokalemia, and increased activity in alkaline phosphatase and alanine aminotransferase have been reported (Leifer et al, 1986), but these findings are considered nonspecific and not helpful in achieving a definitive diagnosis. A correlation has not been established between increased liver enzyme activity and obvious metastasis of beta-cell tumors to the liver.

The only consistent abnormality identified in serum biochemistry profiles is hypoglycemia. The mean initial blood glucose concentration in 123 of our dogs at UC Davis with an insulin-secreting tumor was 42 mg/dL, with a range of 15 to 78 mg/dL (0.84 to 4.4

BOX 9-3 A Partial Listing of the Numerous Disorders that may Result in Weakness

Neuromuscular Disorders

Infectious (e.g., canine distemper, bacterial, mycotic)
 Inflammatory
 Neoplasia
 Cerebrovascular hemorrhage
 Spinal disorders (e.g., type II disc disease; discospondylitis)
 Degenerative myelopathy
 Myasthenia gravis
 Peripheral neuropathy
 Polymyopathy/polymyositis

Polyarthritis

Immune-mediated
 Infectious (e.g., rickettsial)
 Degenerative

Cardiorespiratory

Congestive heart failure
 Tachyarrhythmias/bradyarrhythmias
 Heartworm disease
 Bacterial endocarditis
 Pneumonia (viral, bacterial, mycotic)
 Pleural effusions

Hematologic Disorders

Anemia
 Polycythemia
 Hemangiosarcoma
 Coagulopathy (e.g., warfarin-induced)

Metabolic Disorders

Hypoglycemia
 Hypokalemia
 Hyperkalemia
 Hypercalcemia
 Insulinoma
 Hypothyroidism
 Hypoadrenocorticism
 Hyperadrenocorticism
 Pheochromocytoma
 Hepatic encephalopathy

mmol/L). The median blood glucose concentration was 38 mg/dL (2.1 mmol/L). One hundred and eleven of 123 dogs (90%) had a random blood glucose concentration less than 60 mg/dL (3.4 mmol/L). Dogs with insulin-secreting beta-cell tumors may occasionally have a blood glucose concentration between 60 and 70 mg/dL (3.4 and 3.9 mmol/L) on random testing. Such a finding does not eliminate hypoglycemia as a cause of episodic weakness or seizure activity. Fasting, with hourly evaluation of the blood glucose concentration, should be done to induce hypoglycemia in dogs with suspected insulin-secreting beta-cell tumor. The time required to induce hypoglycemia with fasting depends in part on the extent of disease at the time the dog is examined and ranges from a few hours to longer than 24 hours. Hypoglycemia (blood glucose < 60 mg/dL) will develop in most dogs with an insulin-secreting beta-cell tumor within 12 hours of withholding food. A fast of 8 or fewer hours was successful in demonstrating hypoglycemia in 33 of 35 trials in 31 dogs with insulin-secreting tumor (Kruth et al, 1982). We have had a few dogs require 12 to 24 hours of fasting before hypoglycemia became apparent and a

couple of dogs that did not develop hypoglycemia after 30 hours of fasting. The clinical signs in these dogs were episodic and mild, and the diagnosis of beta-cell tumor was not established until 2 to 3 months after initial presentation.



DIFFERENTIAL DIAGNOSES FOR FASTING HYPOGLYCEMIA

Hypoglycemia is present if the blood glucose concentration is less than 60 mg/dL (3.4 mmol/L). It typically results from the excessive uptake of glucose by normal cells (e.g., during periods of hyperinsulinism, such as that which occurs with a beta-cell tumor or xylitol ingestion) or neoplastic cells, impaired hepatic gluconeogenesis and glycogenolysis (e.g., portal shunt, hepatic cirrhosis), a deficiency in diabetogenic hormones (e.g., hypocortisolism), an inadequate dietary intake of glucose and other substrates required for hepatic gluconeogenesis (e.g., anorexia in the neonate or toy breeds), or a combination of these mechanisms (e.g., sepsis; [Box 9-4](#); [Service, 1995](#)). Iatrogenic hypoglycemia is a

BOX 9-4 Causes of Hypoglycemia in Dogs and Cats

Beta-cell tumor (insulinoma)*
 Extra pancreatic neoplasia (see [Box 9-5](#))
 Hepatocellular carcinoma, hepatoma*
 Leiomyosarcoma, leiomyoma*
 Hepatobiliary disease*
 Portosystemic shunts
 Chronic fibrosis, cirrhosis
 Hepatic necrosis; toxins, infectious agents
 Primary and metastatic neoplasia
 Sepsis*
 Severe canine babesiosis
 Septic peritonitis
 Hypoadrenocorticism*
 Primary and secondary
 Idiopathic hypoglycemia*
 Neonatal hypoglycemia
 Juvenile hypoglycemia (especially toy breeds)
 Hunting dog hypoglycemia
 Exocrine pancreatic neoplasia
 Pancreatitis
 Glucagon deficiency (?)
 Chronic kidney disease
 Hypopituitarism
 Severe polycythemia
 Hepatic enzyme deficiencies
 Glycogen storage diseases (GSDs)
 Severe malnutrition
 Prolonged storage of whole blood*
 Iatrogenic
 Insulin overdose*
 Sulfonylurea therapy
 Ethylene glycol ingestion
 Xylitol ingestion
 Alpha lipoic acid
 Dried chicken jerky treats
 Artifact*
 Portable blood glucose monitoring (PBGm) devices
 Laboratory error

*Common cause.

common problem resulting from overzealous insulin administration in diabetic dogs and cats.

Congenital Hepatic Disease

Portovascular anomalies are the most common congenital cause of hepatic-induced hypoglycemia. Hypoglycemia develops despite an appropriate reduction in circulating insulin because of insufficient hepatic glycogen stores and inadequate hepatocellular function to support gluconeogenesis. Abnormalities suggestive of this disorder include microcytosis, hypoalbuminemia, hypocholesterolemia, decreased urea nitrogen, increased total bilirubin, ammonium biurate crystals in the urine, abnormal preprandial and postprandial bile acid concentrations, and small liver size on abdominal radiography or ultrasonography. Confirmatory tests include liver biopsy, angiography, nuclear scintigraphy, and identification of the shunt during abdominal ultrasound, computed tomography (CT) scanning or exploratory celiotomy.

Glycogen storage diseases (GSDs) are rare autosomal recessive disorders of glycogen metabolism that result from a congenital absolute or relative deficiency of one of the enzymes necessary to convert glycogen to glucose. In dogs, four breed-specific types of GSD have been described. Type Ia in Maltese terriers (von Gierke disease) is a deficiency in glucose-6-phosphatase caused by a mutated, defective glucose-6-phosphatase gene ([Brix et al, 1995](#); [Kishnani et al, 1997](#); [2001](#)). Type II in Lapland dogs (Pompe disease) is a deficiency of lysosomal acid α -glucosidase ([Walvoort et al, 1985](#)). Type III in German Shepherd dogs and Curly-Coated Retrievers (Cori disease) is a deficiency of glycogen debranching enzyme (amylo-1,6-glucosidase; [Fig. 9-4](#)) ([Hardy, 1989](#); [Gregory et al, 2007](#)). GSD in Curly-Coated Retrievers affects both liver and muscle (GSD type IIIa) and is caused by a mutation of the glycogen debranching enzyme gene (*AGL*) ([Gregory et al, 2007](#)). Type VII in English Springer Spaniels (Tarui disease) is a deficiency in phosphofructokinase ([Giger et al, 1988](#); [Smith et al, 1996](#)). In cats, GSD type IV has been identified in Norwegian Forest cats, is caused by a deficiency in a glycogen branching enzyme (alpha-1,4 glucan 6 glycol transferase), and results in glycogen accumulation in skeletal and cardiac muscle and the nervous system ([Fyfe et al, 1992](#)).

Indicators for possible GSD in a juvenile dog include: clinical signs suggestive of hypoglycemia; progressive hepatomegaly characterized histologically by diffuse, marked hepatocellular vacuolation caused by glycogen accumulation; and hypoglycemia and increased hepatic enzyme activities identified on routine blood and urine tests. Serum glucose concentrations typically fail to increase after injection of glucagon in dogs with type Ia and type III GSDs. Confirmatory tests include histologic evaluation of hepatic biopsies and specific hepatic enzyme assays.

Acquired Hepatic Dysfunction

Hypoglycemia may result from progressive and severe destruction of the liver typically caused by primary or metastatic neoplasia or chronic inflammation leading to fibrosis, cirrhosis, and the development of acquired hepatic vascular shunts. There are numerous potential causes of chronic hepatic fibrosis in older dogs and cats. Hypoglycemia results from inadequate amounts of functional hepatic tissue for adequate storage of glycogen or for sufficient gluconeogenesis to sustain a normal blood glucose concentration during a fast. Serum insulin concentrations decline appropriately with worsening hypoglycemia, but this alone may be insufficient to prevent problems. Additional abnormalities suggestive of hepatic insufficiency include microcytosis, hypoalbuminemia,

hypcholesterolemia, decreased urea nitrogen, increased total bilirubin, ammonium biurate crystals in the urine, abnormal preprandial and postprandial bile acid concentrations, abnormal liver size on abdominal radiography, or abnormal echotexture or liver size on ultrasonography. Liver biopsy is helpful in confirming severe fibrosis or cirrhosis and may even identify a cause (e.g., neoplasia). The etiology of hepatic fibrosis and cirrhosis goes undiagnosed in most cases.

Adrenocortical Insufficiency (Addison’s Disease)

Hypoglycemia in dogs with hypoadrenocorticism is caused by insufficient secretion of the glucocorticoids needed to stimulate hepatic mobilization and production of glucose (see Chapter 12). In this disorder, hypoglycemia occurs despite an appropriate reduction in the blood insulin concentration. Reduced insulin secretion must be accompanied by an increase in hepatic gluconeogenesis to correct hypoglycemia. Glucose synthesis is normally stimulated by gluconeogenic hormones. Without secretion of these hormones, as observed in hypoadrenocorticism, hypoglycemia is possible (Sherwin and Felig, 1981). Hypoadrenocorticism is most common in young and middle-aged dogs, and there is a gender predisposition for the female. Abnormalities on screening tests supportive of this diagnosis include a relative increase in the eosinophil and lymphocyte counts, mild nonregenerative anemia, mild to severe prerenal azotemia, hyperkalemia, hyponatremia, and hypercalcemia. Hypoglycemia may also develop with atypical hypoadrenocorticism, which is characterized by cortisol but not mineralocorticoid deficiency and normal serum electrolyte concentrations. The diagnosis of hypoadrenocorticism can be confirmed by abnormal results on adrenocorticotrophic hormone (ACTH) stimulation test.

Glucagon Deficiency

Glucagon is the key counterregulatory hormone affecting recovery from acute hypoglycemia (Cryer and Gerich, 1985). In response to falling plasma glucose concentrations, glucagon is secreted by the alpha cells of the pancreatic islets into the hepatic portal

circulation, and it acts exclusively on the liver to activate glycogenolysis and gluconeogenesis (Cryer and Polonsky, 1998). Hepatic glucose production is increased almost immediately. Abnormalities in the production or secretion of glucagon prevent a normal counterregulatory response to decreasing blood glucose concentrations and predispose the animal to hypoglycemia. A classic example is hypoglycemia unawareness in diabetic humans, which is a syndrome caused by deficient glucagon and catecholamine secretion, resulting in defective counterregulation, severe hypoglycemia, and diabetic coma (Gerich et al, 1991; Mokan et al, 1994; Meyer et al, 1998). Isolated glucagon deficiency that causes hypoglycemia has been reported in humans but is rare (Cryer and Polonsky, 1998). Typically, glucagon deficiency occurs in conjunction with excess insulin secretion, deficient catecholamine secretion, or increased tissue sensitivity to the actions of insulin; and this combination results in hypoglycemia. We have identified hypoglycemia in dogs and cats with severe pancreatitis and exocrine pancreatic adenocarcinoma, and we speculate that the destructive process associated with these disorders may alter the production and/or secretion of glucagon and insulin.

Hypopituitarism

GH and cortisol are glucose counterregulatory hormones involved in hepatic glucose synthesis and secretion. Failure of the pituitary gland to secrete ACTH, GH, or both may impact maintenance of glucose homeostasis and predispose the animal to hypoglycemia, especially in the fasting state. As in primary hypoadrenocorticism, insulin secretion diminishes appropriately for the degree of hypoglycemia, but this alone may not be sufficient to prevent clinical signs. GH deficiency is a rare cause of hypoglycemia and is usually diagnosed in young German Shepherd dogs as a congenital defect (see Chapter 2). Pituitary failure to secrete ACTH results in atrophy of the zona fasciculata of the adrenal cortex, impaired secretion of cortisol, and the development of secondary hypoadrenocorticism. No classic abnormalities are found on screening laboratory studies in animals with secondary hypoadrenocorticism. These dogs may have a mild nonregenerative anemia and fasting hypoglycemia, but serum electrolyte concentrations are

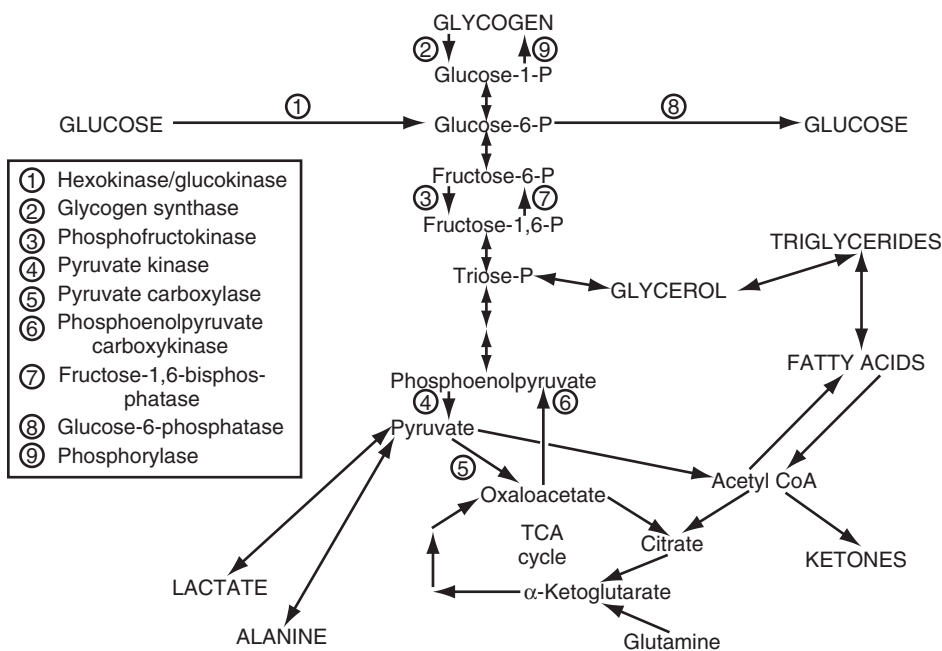


FIGURE 9-4 Schematic representation of glucose metabolism. (From Cryer PE, Polonsky KS: In Wilson JD, et al, editors: *Williams textbook of endocrinology*, ed 9, Philadelphia, 1998, WB Saunders, p. 940.) Acetyl CoA, Acetyl coenzyme A; TCA, tricarboxylic acid.

usually normal. An ACTH stimulation test and determination of a baseline endogenous ACTH concentration are used to establish the diagnosis of secondary hypoadrenocorticism (see Chapter 12).

Non-Beta-Cell Tumors

In humans, non-beta-cell tumors that cause hypoglycemia are usually of mesenchymal origin (e.g., leiomyosarcoma, fibrosarcoma). Hypoglycemia is caused less often by tumors of epithelial origin (e.g., hepatoma, carcinoid tumors) and hematopoietic origin (e.g., lymphoma, multiple myeloma) (Cryer and Polonsky, 1998). A variety of tumor types have also been reported to cause hypoglycemia in the dog (Box 9-5). In our hospital, hepatocellular carcinoma, hepatoma, leiomyoma, leiomyosarcoma, and tumors with extensive hepatic metastasis are most commonly associated with hypoglycemia (Cohen et al, 2003).

The pathogenesis of hypoglycemia associated with non-beta-cell tumors is undoubtedly multifactorial. Proposed mechanisms include excessive glucose utilization by the tumor, impaired hepatic glycogenolysis and gluconeogenesis as a result of tumor-induced hepatic destruction or inhibition of normal counter-regulatory responses that prevent hypoglycemia, and secretion of an insulin-like molecule, specifically insulin-like growth factor-2 (IGF-2) that lowers the blood glucose concentration by enhancing glucose utilization by normal cells (Cryer and Polonsky, 1998). Although the major organ responsible for circulating insulin-like growth factors is the liver, it has been demonstrated that these factors are produced ubiquitously, particularly by mesenchymal cells (D'Ercole et al, 1984; Barreca et al, 1992). IGF-2 is structurally homologous to proinsulin, can bind to insulin receptors, and has direct insulin-like actions that result in hypoglycemia (de Groot et al, 2007). In addition, IGF-2 may suppress glucagon and GH secretion, which may also contribute to hypoglycemia (Cryer and Polonsky, 1998). Serum insulin concentrations are typically undetectable or in the lower end of the reference range with non-beta-cell tumors, in contrast to the high-normal to increased serum insulin concentrations seen with hypoglycemia induced by a beta-cell tumor (Beaudry et al, 1995; Bagley et al, 1996; Bellah and Ginn, 1996).

Paraneoplastic hypoglycemia affiliated with IGF-2 secretion has been reported in a dog with gastric leiomyoma, mammary

carcinoma, hepatocellular carcinoma, and pancreatic neuroendocrine tumor (Boari et al, 1995; Zini et al, 2007; Finotello et al, 2009; Rossi et al, 2010). Blood glucose and serum insulin concentrations were low and serum IGF-2 concentrations were increased at presentation to the veterinary hospital in all dogs. Blood glucose and serum IGF-2 concentrations returned to the reference range in three dogs that underwent surgical removal of the tumor and results of immunohistochemical staining of tumor tissue were positive for IGF-2 in all four dogs. Interestingly, the dog with an IGF-2-secreting mammary carcinoma was an insulin-dependent diabetic dog prior to development of the mammary carcinoma; this dog developed problems with severe hypoglycemia as the tumor enlarged and became diabetic again after surgical removal of the tumor (Rossi et al, 2010).

In another study involving four dogs with hypoglycemia caused by smooth muscle tumors, the results of immunohistochemical staining for insulin were negative in the four tumors but positive for glucagon in three of the four tumors (Beaudry et al, 1995). The three smooth muscle tumors that stained positive for glucagon originated in either the stomach or jejunum, whereas the tumor that stained negative for glucagon originated in the spleen. Immunohistochemical staining for glucagon was negative in smooth muscle cells in normal adjacent tissue. The clinical relevance of this finding remains unclear, especially considering that glucagon should increase, not decrease, the blood glucose concentration.

Dogs with hypoglycemia caused by a non-beta-cell tumor may be brought to the veterinarian with clinical signs of hypoglycemia, or hypoglycemia may be a serendipitous finding on a serum biochemistry panel. In most dogs, non-beta-cell tumors that cause hypoglycemia are located in the liver or abdomen. Identification of a non-beta-cell tumor requires a thorough physical examination of the dog or cat, thoracic and abdominal radiography, abdominal ultrasonography, and histopathologic evaluation of biopsy specimens from identifiable masses. The association between a non-beta-cell tumor and hypoglycemia requires resolution of hypoglycemia after surgical excision of the tumor.

Neonatal and Juvenile Hypoglycemia

The fetus receives a continuous source of glucose via the placenta and does not depend on its own gluconeogenic capabilities to maintain an adequate blood glucose concentration. In contrast, the neonate depends on glycogenolysis and gluconeogenesis to maintain euglycemia during fasts, even if brief. Limited hepatic glycogen stores, small muscle mass, lack of adipose tissue, and decreased use of free fatty acids as an alternative energy source place the neonate at risk for developing hypoglycemia within hours of fasting (Chastain, 1990). Impaired gluconeogenesis as a result of delayed induction of one or more of the rate-limiting gluconeogenic enzymes is suspected in neonatal hypoglycemia of human infants (Cryer and Polonsky, 1998) and may play a role in neonatal hypoglycemia of puppies and kittens as well.

Hypoglycemia often occurs in conjunction with hypothermia, sepsis, starvation, toxic milk syndrome, or a combination of these problems. The ill neonate should always be evaluated for hypoglycemia. Orally administered glucose (e.g., 0.01 mL of 5% to 10% solution per gram of body weight) and frequent nursing or bottle feeding help correct and prevent hypoglycemia in the neonate.

Hypoglycemia of toy and miniature breed dogs younger than 6 months of age is common. Alanine deficiency has been implicated in this syndrome, as it has in young children (Chew et al, 1982). In humans, the rate of alanine release from muscle determines the rate of gluconeogenesis during starvation. Puppies with juvenile

BOX 9-5 Histologic Classification of Non-Beta-Cell Tumors Associated with Hypoglycemia

Hepatocellular carcinoma, hepatoma
 Leiomyosarcoma, leiomyoma
 Hemangiosarcoma
 Adenocarcinoma
 Mammary
 Nasal (horse)
 Pulmonary
 Salivary
 Gastric
 Small intestine
 Splenic
 Renal
 Lymphoblastic leukemia
 Plasmacytoma
 Metastatic melanoma
 Pancreatic neuroendocrine tumor

hypoglycemia are usually under extreme stress. They frequently have a history of recently being purchased, with an associated change in environment and diet. Gastrointestinal upset (vomiting, diarrhea, and/or anorexia) is typical and may or may not be associated with parasites. These puppies are quite fragile and are brought to veterinarians with signs that may include weakness, collapse, depression, ataxia, stupor, convulsions, hypothermia, and/or diarrhea. IV administration of glucose usually results in rapid clinical improvement. Frequent feedings prevent recurrences. This disorder virtually disappears with attainment of adult height and weight. If signs persist, a search for another disease that may be causing the hypoglycemia should be considered.

Endotoxic or Sepsis-Induced Hypoglycemia

Endotoxic or sepsis-induced hypoglycemia is a relatively uncommon cause of hypoglycemia in the dog and cat (Breitschwerdt et al, 1981). The pathogenesis of sepsis-induced hypoglycemia is not well characterized but is believed to result from increased tissue utilization of glucose in conjunction with decreased hepatic glucose production (Naylor and Kronfeld, 1985; Hargrove et al, 1988a; 1988b). Proposed mechanisms for increased glucose utilization include sepsis-induced production of insulin-like substances, interleukin-1-enhanced insulin secretion by beta cells, cytokine-enhanced increase in glucose transport into cells, and increased glucose utilization by bacteria and neutrophils (Commens et al, 1987; del Rey and Besedovsky, 1987). Increased glucose use by macrophage-rich tissues (e.g., the liver, spleen, and ileum) is responsible for most of the glucose utilization (Meszaros et al, 1988), with skeletal muscle accounting for an additional 25% (Meszaros et al, 1987). Decreased hepatic glucose production may result from impaired hepatic oxidative metabolism, increased anaerobic glycolysis of liver glucose, hypoxic injury to hepatic cells, or sepsis-induced interference with substrate delivery to the liver (see Feldman and Nelson [1987] for references). Endotoxin may also decrease glycogenolysis through depletion of hepatic and muscle glycogen stores and may impair hepatic gluconeogenesis.

In our hospital, sepsis-induced hypoglycemia is most commonly associated with parvovirus infection, abscesses, hemorrhagic gastroenteritis, pyothorax, pyometra, and gram-negative septicemia. Sepsis-induced hypoglycemia should be considered if a hypoglycemic animal is suffering from severe infection or significant leukocytosis (> 30,000 cells/ μ L). Artfactual hypoglycemia caused by delays in measuring the glucose concentration in a blood sample containing bacteria and marked leukocytosis may contribute to the low blood glucose measurement. A diagnosis of sepsis-induced hypoglycemia is based on identification of infection by means of a physical examination, CBC, radiography and ultrasonography, appropriate bacterial cultures, and resolution of hypoglycemia after initiation of appropriate antibiotic therapy. If severe infection is diagnosed in a dog or cat with hypoglycemia, pursuit of other causes of hypoglycemia is usually not warranted unless screening tests dictate otherwise or the hypoglycemia fails to resolve after initiation of appropriate antibiotic therapy.

Kidney Failure

The blood glucose concentration in dogs and cats with kidney failure is usually within the reference range. Occasionally dogs and cats develop hyperglycemia as a result of uremia-induced carbohydrate intolerance and insulin resistance or more commonly develop problems with glycemic control in a dog or cat with concurrent diabetes mellitus. Although critical illness caused by kidney failure

may cause hypoglycemia in humans, kidney failure-induced hypoglycemia is a very uncommon finding in dogs and cats (Edwards et al, 1987; Cryer, 2011). Proposed mechanisms for development of hypoglycemia in kidney failure include decreased renal gluconeogenesis in conjunction with impaired glucose production by the liver as a consequence of defective hepatic glycogenolysis and gluconeogenesis, limited availability of glucogenic substrates, inadequate glucose counterregulatory responses, decreased caloric intake, decreased renal degradation, and/or excretion of insulin (Fischer et al, 1986; Gerich et al, 2001).

Polycythemia

Severe polycythemia (hematocrit > 65%) may cause artifactual hypoglycemia secondary to increased glucose utilization by the markedly increased number of red blood cells in the blood sample. Polycythemia may be primary (i.e., polycythemia vera), or it may occur secondary to disorders that cause chronic systemic hypoxia (e.g., congenital right-to-left shunting of blood in the heart), to chronic renal hypoxia (e.g., renal neoplasia), or to erythropoietin-producing tumors.

Artfactual Hypoglycemia

Prolonged storage of blood before separation of serum or plasma causes the glucose concentration to decrease at a rate of approximately 7 mg/dL/h (0.4 mmol/L/h). Glycolysis by red and white blood cells becomes even more apparent in dogs and cats with erythrocytosis, leukocytosis, or sepsis. Therefore whole blood obtained for the measurement of the glucose concentration should be separated soon after collection (within 30 minutes), and the serum or plasma should be refrigerated or frozen until the assay is performed to minimize artifactual lowering of the blood glucose concentration. Glucose determinations from separated and refrigerated plasma or serum are reliable for as long as 48 hours after the separation and refrigeration of the specimen. Alternatively, plasma can be collected in sodium fluoride tubes; sodium fluoride inhibits glycolysis by erythrocytes, leukocytes, and platelets. Unfortunately, hemolysis is common in blood collected in sodium fluoride-treated tubes, which can result in slight decrements in glucose values owing to methodological problems in laboratory determinations.

Blood glucose values determined by many portable blood glucose monitoring (PBGGM) devices designed for use by human diabetics are almost always lower than actual glucose values determined by bench-top methodologies (e.g., glucose oxidase and hexokinase methods). A notable exception is the AlphaTRAK glucometer designed for use in diabetic dogs and cats. Blood glucose values obtained with the AlphaTRAK can be high or low compared with actual glucose values (Cohen et al, 2009; Zini et al, 2009; Fig. 9-5). Failure to consider this "error" when using a PBGM device could result in an incorrect diagnosis of hypoglycemia. Fortunately, for most PBGM devices, the more severe the hypoglycemia, the more accurate the device becomes.

Laboratory error may also result in an incorrect value for any assay. Therefore it is wise to confirm a finding of hypoglycemia by means of evaluation of a second blood sample using bench-top methodology before more expensive studies are performed to identify the cause of hypoglycemia.

Iatrogenic Hypoglycemia (Toxicities)

Insulin and oral sulfonylurea drugs (e.g., glipizide, glyburide) are the only commonly available drugs that consistently lower the

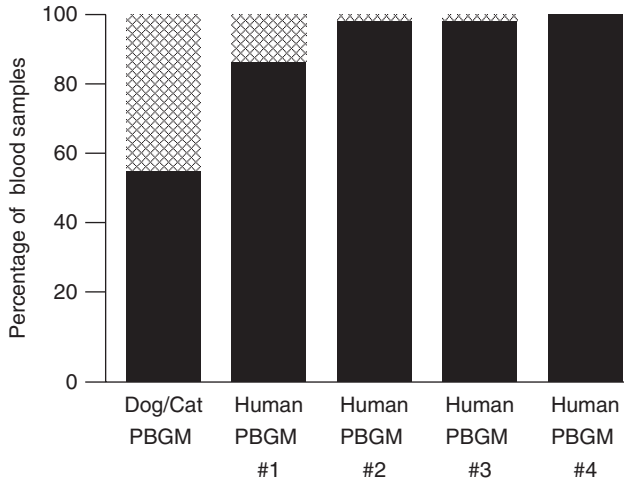


FIGURE 9-5 Frequency of low (solid) and high (hatched) blood glucose results measured in the same blood sample by five portable blood glucose monitoring (PBGM) meters designed for use in human diabetics and one meter (AlphaTRAK) designed for use in diabetic dogs and cats, compared with reference analyzer results. One hundred fifty-eight blood samples obtained from 49 dogs were evaluated. Blood glucose concentrations measured by the reference analyzer ranged from 41 to 639 mg/dL (2.3 to 35.8 mmol/L). (From Cohen TA, et al.: Evaluation of six portable blood glucose meters for measuring blood glucose concentration in dogs, *J Am Vet Med Assoc* 235:279, 2009.)

blood glucose concentration. In small animal practice, the most common cause of symptomatic hypoglycemia is an overdose of insulin in a diabetic dog and cat—a diagnosis that should always be suspected whenever a client reports signs resembling hypoglycemia in a diabetic pet.

Clinical hypoglycemia has been reported in dogs following the ingestion of alpha lipoic acid (Loftin and Herold, 2009), dried chicken jerky treats (Hooper and Roberts, 2011; Thompson et al, 2013), and xylitol (Murphy and Coleman, 2012). Alpha lipoic acid has antioxidant properties, is available as an over-the-counter supplement, and has been investigated as possible adjunctive treatment for various conditions, including diabetes mellitus and diabetic neuropathy. Ingestion of dried chicken jerky treats made in China caused Fanconi syndrome characterized by glucosuria and euglycemia or hypoglycemia in addition to lethargy, inappetence, and vomiting in dogs. Xylitol is a five-carbon sugar alcohol used as a sweetener and sugar substitute in many products including chewing gums, candies, baked goods, jellies, drink powders, vitamins, and nutritional supplements (Murphy and Coleman, 2012). Xylitol ingestion in dogs stimulates insulin secretion leading to potentially severe and life-threatening hypoglycemia, which may develop within 30 minutes to 12 hours after xylitol ingestion. Acute hepatic failure may develop 1 to 3 days later. Treatment for these toxicities included IV fluids with dextrose administration in addition to supportive care.



DIAGNOSTIC APPROACH TO HYPOGLYCEMIA: PRIORITIZING THE DIFFERENTIALS

Hypoglycemia should always be confirmed in a second blood sample before initiating diagnostic studies to identify the cause. Careful evaluation of the animal's history, physical examination findings, and results of routine blood and urine tests (i.e., CBC, serum biochemistry panel, and urinalysis) usually provide clues to the underlying cause. Hypoglycemia in the puppy or kitten is

usually caused by idiopathic hypoglycemia, starvation, congenital portosystemic shunt, or sepsis. In young adult dogs or cats, hypoglycemia is usually caused by hepatobiliary disease, portosystemic shunt, hypoadrenocorticism, or sepsis. In older dogs or cats, hepatobiliary disease, beta-cell neoplasia, extrapancreatic neoplasia, hypoadrenocorticism, and sepsis are the most common causes.

The blood glucose concentration tends to be greater than 45 mg/dL (2.5 mmol/L) and is often an incidental finding in dogs and cats with hypoadrenocorticism or hepatobiliary disease, although severe hypoglycemia causing neurologic signs may occasionally occur. Additional clinical pathologic alterations are usually present (e.g., hyponatremia and hyperkalemia in animals with hypoadrenocorticism or increased liver enzyme activities, hypocholesterolemia, hypoalbuminemia, and a low blood urea nitrogen [BUN] concentration in animals with hepatobiliary disease). Normal serum electrolyte concentrations do not rule out a cortisol deficiency as the cause for hypoglycemia; atypical hypoadrenocorticism may be present. An ACTH stimulation test or liver function test (i.e., preprandial and postprandial bile acids) may be required to confirm the diagnosis. Severe hypoglycemia (less than 40 mg/dL; 2.2 mmol/L) may develop in neonates and juvenile kittens and puppies (especially toy breeds) and in animals with sepsis, beta-cell neoplasia, and extrapancreatic neoplasia—most notably hepatic adenocarcinoma and leiomyosarcoma. Sepsis is readily identified on the basis of physical examination findings and abnormal CBC findings, which include a neutrophilic leukocytosis (typically > 30,000/ μ L), a shift toward immaturity, and signs of toxicity. Extrapancreatic neoplasia can usually be identified on the basis of the physical examination, abdominal or thoracic radiography, and abdominal ultrasonography findings. Dogs with beta-cell neoplasia typically have normal physical examination findings aside from findings suggestive of hypoglycemia (e.g., weakness) and no abnormalities other than hypoglycemia identified on routine blood and urine tests. Measurement of baseline serum insulin concentration when the blood glucose is less than 60 mg/dL (3.4 mmol/L) is used to confirm the diagnosis of a beta-cell tumor.



CONFIRMING THE DIAGNOSIS OF AN INSULIN-SECRETING BETA-CELL TUMOR: SERUM INSULIN DETERMINATION

The diagnosis of an insulin-secreting beta-cell tumor requires an initial confirmation of hypoglycemia followed by documentation of inappropriate insulin secretion and identification of a pancreatic mass using ultrasonography, CT, or exploratory celiotomy. Considering the potential differential diagnoses for hypoglycemia (see Box 9-4), a tentative diagnosis of insulin-secreting beta-cell tumor can often be made on the basis of the history, physical examination findings, and an absence of abnormalities other than hypoglycemia shown by routine blood tests.

Whipple's Triad

In 1935, the report that established insulin-secreting tumors of the pancreas as a clinical entity included a discussion of the three criteria to be used in confirming the diagnosis (Whipple and Grantz, 1935). These standards, now referred to as *Whipple's triad*, are: (1) the symptoms occur after fasting or exercise; (2) at the time of symptoms, the serum glucose concentration is less than 50 mg/dL (2.8 mmol/L); and (3) the symptoms are relieved by administration of glucose. Unfortunately, this triad can result from numerous causes of hypoglycemia and as such is nonspecific.

Determination of Baseline Insulin and Glucose Concentrations

Theory

The diagnosis of an insulin-secreting beta-cell tumor is established by evaluating the blood insulin concentration at a time when hypoglycemia is present. Hypoglycemia suppresses insulin secretion in normal animals, with the degree of suppression directly related to the severity of the hypoglycemia. Hypoglycemia fails to have this same suppressive effect on insulin secretion if the insulin is synthesized and secreted from autonomous neoplastic cells, because tumor cells that produce and secrete insulin are less responsive to hypoglycemia than normal beta cells. Invariably the dog with an insulin-secreting tumor will have an inappropriate excess of insulin relative to that needed for a particular blood glucose concentration. The relative excess of insulin is easiest to recognize when the blood glucose concentration is low, preferably less than 50 mg/dL (2.8 mmol/L). If the blood glucose concentration is low and the insulin concentration is in the upper half of the reference range or increased, the dog has a relative or absolute excess of insulin that can be explained by the presence of an insulin-secreting tumor that is insensitive to hypoglycemia. Confidence in identifying an inappropriate excess of insulin depends on the severity of the hypoglycemia; the lower the blood glucose concentration, the more confident the clinician can be in identifying inappropriate hyperinsulinemia, especially when the serum insulin concentration falls in the reference range.

Protocol

Most dogs with insulin-secreting neoplasia are persistently hypoglycemic. If the blood glucose concentration is less than 60 mg/dL (3.4 mmol/L) and preferably less than 50 mg/dL (2.8 mmol/L), serum should be submitted to a commercial veterinary endocrine laboratory for determination of the glucose and insulin concentrations. The insulin assay must be validated for use in dogs, and interpretation of insulin results should be based on the reference interval established by the laboratory utilized (Madarama et al, 2009; Öberg et al, 2011). If the dog's blood glucose concentration is greater than 60 mg/dL, fasting may be necessary to induce hypoglycemia. Blood glucose concentrations should be evaluated hourly during the fast and blood obtained for glucose and insulin determination when the blood glucose concentration is less than 60 mg/dL. It is important to remember that blood glucose results obtained from PBGM devices are often lower than results obtained using bench-top methodologies (Cohn et al, 2000; Wess and Reusch, 2000; Cohen et al, 2009; Zini et al, 2009). Ideally a blood sample for submission to a commercial laboratory for glucose and insulin determinations should not be obtained until the blood glucose measured on these devices is less than 50 mg/dL. Once fasting has induced hypoglycemia and the blood sample has been obtained for glucose and insulin determination, the dog can be fed several small meals over the next 2 to 3 hours to minimize overstimulation of the tumor and rebound hypoglycemia.

Interpretation

The serum insulin concentration must be evaluated from the same blood sample as and in relation to the blood glucose concentration (Box 9-6). A serum insulin concentration that exceeds the upper limit of the reference range in a dog with a corresponding blood glucose concentration of less than 60 mg/dL (3.4 mmol/L), in combination with appropriate clinical signs and clinical pathologic findings, strongly supports the diagnosis of an insulin-secreting tumor. An insulin-secreting tumor is also possible if the serum

BOX 9-6 Interpretation of Baseline Serum Insulin Concentration in Dogs with Hypoglycemia Believed to be Caused by Insulin-Secreting Beta-Cell Neoplasia

SERUM INSULIN CONCENTRATION	PROBABILITY OF BETA-CELL TUMOR*
Above reference range	High
Upper half of reference range	Possible
Lower half of reference range	Low
Below reference range	Ruled out

*Ideally, the blood glucose concentration determined by a bench-top methodology (i.e., glucose oxidase or hexokinase method) should be less than 50 mg/dL in the same blood sample submitted to the laboratory for insulin determination. Interpretation of serum insulin concentration is unreliable if the blood glucose concentration is greater than 60 mg/dL.

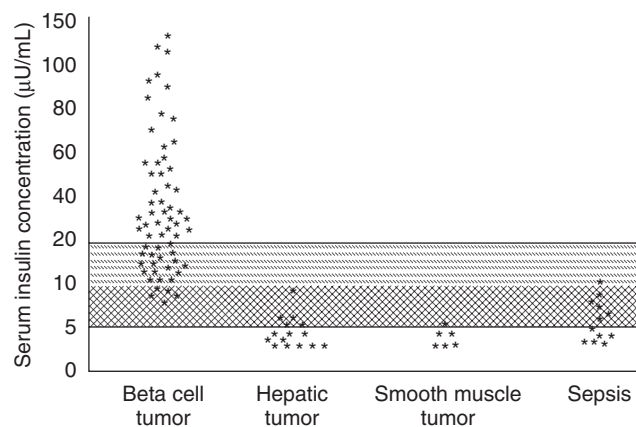


FIGURE 9-6 Serum insulin concentrations in dogs with hypoglycemia caused by an insulin-secreting beta-cell tumor, hepatoma or hepatocellular carcinoma, leiomyosarcoma, or sepsis. Although a serum insulin concentration in the high end of the normal range (i.e., > 10 µU/mL) is consistent with a beta-cell tumor, a serum insulin concentration in the low end of the normal range (i.e., 5 to 10 µU/mL) is not diagnostic for a beta-cell tumor. Shaded regions represent the high (horizontal lines) and low (hatched area) ends of the normal range.

insulin concentration is in the upper half of the reference range. Insulin values near the lower end of the reference range may be found in animals with other causes of hypoglycemia, as well as in those with insulin-secreting tumors (Fig. 9-6). Careful assessment of the history, physical examination findings, and diagnostic test results in relation to viable differentials for hypoglycemia in that dog and, if necessary, repeating serum glucose and insulin measurements when hypoglycemia is more severe will usually identify the cause of the hypoglycemia. In 101 of our dogs with a histologically confirmed beta-cell tumor and a blood glucose concentration less than 60 mg/dL, the serum insulin concentration was above the reference range in 74 dogs (73%); in the upper half of the reference range in 21 dogs (21%); and in the lower end of the reference range in 6 dogs (6%). No dog had a serum insulin concentration less than the reference range. Any serum insulin concentration below the reference range is consistent with insulinopenia and does not indicate the presence of an insulin-secreting tumor.

Insulin-to-Glucose Ratios

Several insulin-to-glucose ratios, including the insulin-to-glucose ratio, the glucose-to-insulin ratio, and the amended insulin-to-glucose ratio, have been recommended to evaluate the interrelationship

between the blood glucose and insulin concentrations and to help establish the diagnosis of insulin-secreting tumor when the laboratory results are ambiguous (e.g., hypoglycemia is marginal and serum insulin concentrations remain in the reference range). Of these ratios, the amended insulin-to-glucose ratio is most commonly used. The amended insulin-to-glucose ratio is determined by entering the blood glucose and serum insulin concentrations in the following formula:

$$\frac{\text{serum insulin } (\mu\text{U/mL}) \times 10}{\text{blood glucose (mg/dL)} - 30}$$

The use of “- 30” in the formula is based on the theory that in normal humans, serum insulin concentrations are undetectable when the blood glucose concentration is less than 30 mg/dL (1.7 mmol/L). Whenever the blood glucose concentration is less than 30 mg/dL, the number 1 is used as the divisor. Extrapolating from the human literature, most authors have suggested that an amended insulin-to-glucose ratio greater than 30 is diagnostic of an insulin-secreting tumor. However, this test is not specific; that is, some dogs with other causes of hypoglycemia may have abnormal amended ratios (Leifer et al, 1986). The most common reason for lack of specificity is a detectable serum insulin concentration, albeit usually in the lower end of the reference range, despite hypoglycemia. This occurs most commonly with hepatic tumors and sepsis. We do not rely on insulin-to-glucose ratios for interpretation of blood insulin and glucose results. Rather, we interpret the absolute serum insulin concentration during hypoglycemia (see Box 9-6) in conjunction with the history, physical findings, and results of routine blood and urine tests.

Serum Fructosamine Concentration

Serum fructosamines are glycosylated proteins found in blood that are used to monitor control of glycemia in diabetic dogs and cats (see Chapters 6 and 7). Fructosamines result from an irreversible, non-enzymatic, insulin-independent binding of glucose to serum proteins and are a marker of the average blood glucose concentration during the circulating lifespan of the protein, which varies from 1 to 3 weeks depending on the protein. The extent of glycosylation of serum proteins is directly related to the blood glucose concentration; the lower the average blood glucose concentration during the preceding 2 to 3 weeks, the lower the serum fructosamine concentration, and vice versa. Serum fructosamine concentrations below the reference range support the existence of significant periods of hypoglycemia and an insulin-secreting tumor, assuming the history and findings on physical examination and routine blood and urine test results are also consistent with the diagnosis. A serum fructosamine concentration below the reference interval may also occur with other disorders that cause prolonged periods of hypoglycemia or that interfere with the assay (see Table 6-8). Documenting a low serum fructosamine concentration in a dog with suspected insulinoma and blood glucose concentrations that remain greater than 60 mg/dL despite fasting provides support for additional diagnostics (e.g., diagnostic imaging) or exploratory surgery (Mellanby and Herbage, 2002).

Provocative Testing

Several tests have been described that use agents that stimulate insulin secretion by normal and neoplastic beta cells; these include the glucagon tolerance test, the oral and IV glucose tolerance test, the tolbutamide tolerance test, and the epinephrine stimulation

test. By evaluating the response of blood glucose and insulin concentrations for a period of time after administration of these agents, a differentiation between normal and neoplastic beta cells can potentially be made. We do not use any of these tests to establish the diagnosis of an insulin-secreting tumor, and they are not recommended. See the first edition of *Canine and Feline Endocrinology and Reproduction* (Feldman and Nelson, 1987) for more information on the use of provocative testing in dogs suspected of having beta-cell neoplasia.



DIAGNOSTIC IMAGING

Diagnostic imaging is indicated to identify a pancreatic mass, to identify metastatic disease, and to localize the site of the mass in the pancreas (e.g., pancreatic body versus pancreatic limb); this information provides support for the diagnosis of a beta-cell tumor and a preliminary assessment of surgical resectability, likelihood of postoperative complications (e.g., pancreatitis), and prognosis. Abdominal ultrasound is widely available and is the initial imaging procedure used to assess the pancreas, peripancreatic tissues, and liver. Advanced diagnostic imaging, specifically dual-phase CT, is currently the most sensitive imaging procedure for identification of the primary mass and metastases and is recommended immediately prior to surgical exploration, if available.

Radiography

Abdominal radiographs are not helpful in establishing the diagnosis of an insulin-secreting tumor, partly because of the location of the pancreas and the small size of most insulin-secreting tumors. Insulin-secreting tumors are typically less than 3 cm in diameter at the time the diagnosis is established. Displacement of viscera or a visible mass in the right cranial quadrant of the abdominal cavity is extremely rare. Thoracic radiographs are of limited help in documenting metastatic disease, primarily because beta-cell tumors rarely metastasize to the lungs until late in the course of the disease. As such, thoracic radiographs are typically negative for metastatic disease when obtained at the time the diagnosis is established, and surgery is contemplated. The most common sites of early metastasis are the liver, regional lymph nodes, and peripancreatic omentum, which are regions where abdominal radiographs are also ineffective in identifying metastatic disease.

Ultrasonography

Abdominal ultrasonography can be used to identify a mass in the region of the pancreas and to look for evidence of potential metastatic disease in the liver and surrounding structures (Fig. 9-7). Because of the small size of most beta-cell tumors and similar echogenicity of the tumor and the adjacent normal pancreas, abdominal ultrasonographic findings are often interpreted as normal, although a pancreatic mass or metastatic lesion can be found at surgery. A normal abdominal ultrasonographic finding does not rule out the diagnosis of a beta-cell tumor.

Ultrasonic detection of a mass lesion in the region of the pancreas helps confirm the suspicion of beta-cell tumor in a dog with appropriate clinical signs and clinical pathologic abnormalities (Fig. 9-8). Identification of mass lesions in the hepatic parenchyma or peripancreatic tissue suggests metastatic disease. Occasionally only the metastatic sites are identified with ultrasound, and the tumor in the pancreas goes undetected. Failure to identify a mass lesion in the region of the pancreas or metastatic sites is common and does not rule out the presence of a beta-cell tumor.

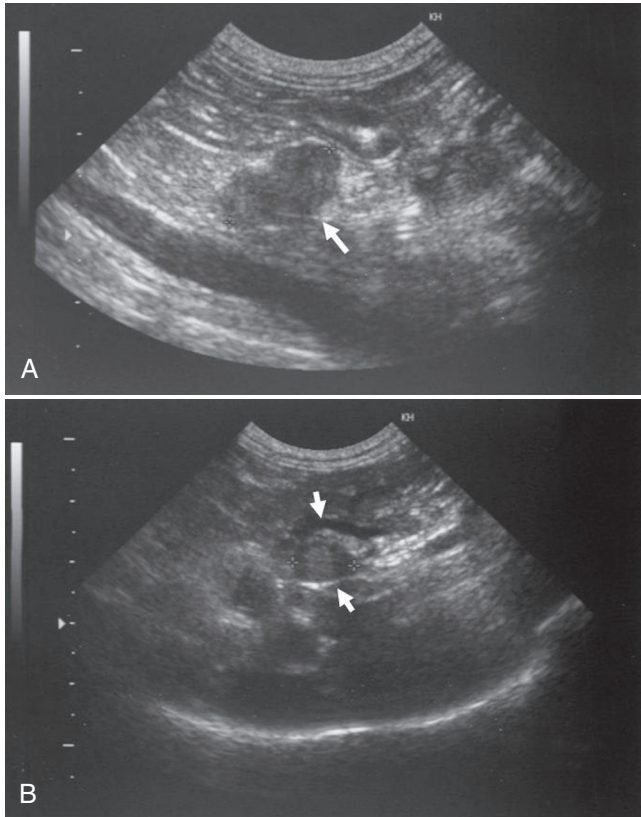


FIGURE 9-7 Ultrasonogram of the pancreas, showing an islet beta-cell tumor (arrow; **A**) and an enlarged hepatic lymph node (arrows; **B**) resulting from metastasis of the beta-cell tumor to the liver in a 9-year-old Cocker Spaniel. (From Nelson RW, Couto CG, editors: *Small animal internal medicine*, ed 5, St Louis, 2014, Elsevier, p. 817.)

In one study evaluating 13 dogs, the sensitivity of ultrasonography for detecting insulinomas was 69% and the sensitivity for detecting hepatic and lymph node metastasis was 44% (Lamb et al, 1995). In a more recent study evaluating 14 dogs, the sensitivity of ultrasonography for detecting insulinomas was 35% and ultrasonography was negative in all five dogs that had lymph node metastasis at surgery, and it was negative in two of four dogs with hepatic metastasis (Robben et al, 2005). Random evaluation of 58 dogs with surgically and histologically confirmed beta-cell neoplasia seen at UC Davis that underwent ultrasound evaluation of the abdomen prior to surgery identified a mass lesion in only 24 dogs (41%). Ultrasonography failed to identify diffuse infiltration of the pancreas by the tumor in two dogs and a mass that was not grossly visible at the time of surgery in two dogs. In one of these dogs, a 2.3 × 1.3 cm pancreatic mass was identified 1 year after the initial exploratory surgery. Tumors in the left limb of the pancreas were identified by ultrasound more often than those in the body or right limb. Similarly, larger tumors were more likely to be identified with ultrasonography although tumors greater than 2 cm × 2 cm were not identified.

The accuracy of ultrasound depends on the experience of the operator, quality of the ultrasound machine and sonogram images, size of the pancreatic mass, and presence of extraneous factors that affect results (e.g., bowel gas, obesity, movement of the dog). Failure to identify a pancreatic mass in a dog suspected of having a beta-cell tumor does not rule out the diagnosis or the presence of metastatic disease but is a further indication for exploratory surgery in the hopes of finding a small, excisable tumor.

Computed Tomography

Conventional pre- and postcontrast CT is reported to have better sensitivity than ultrasonography for the detection of beta-cell

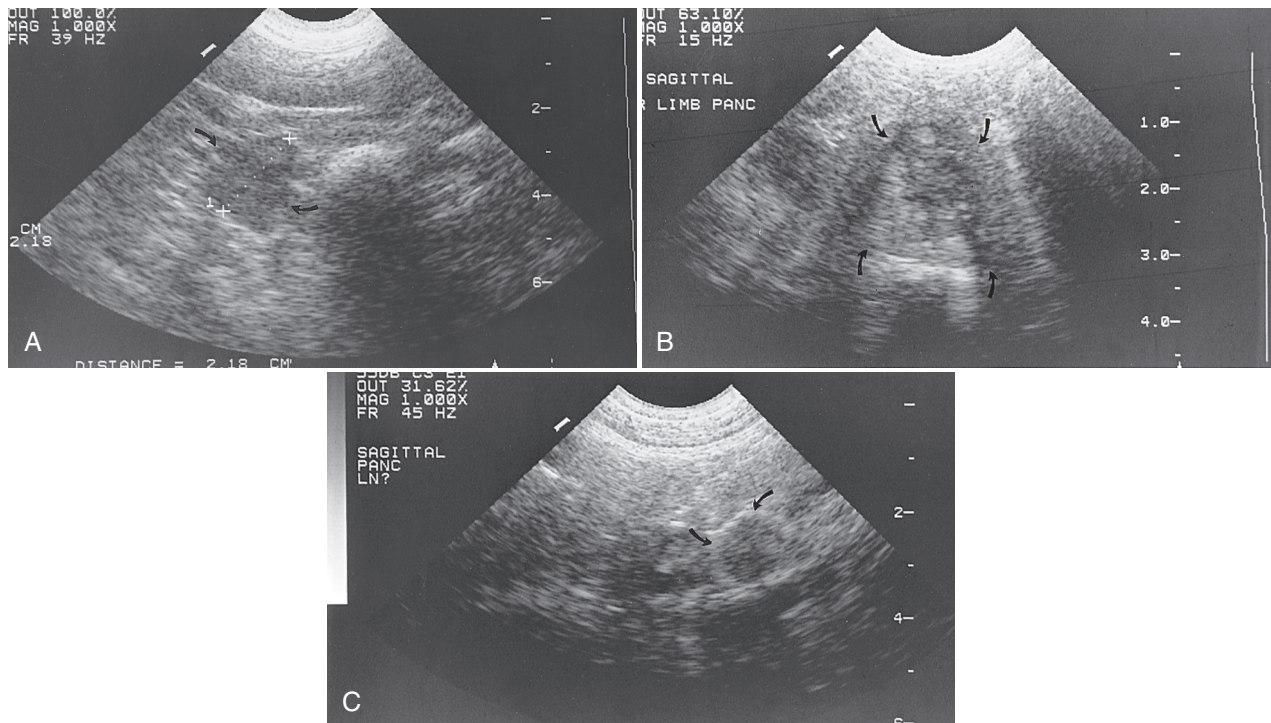


FIGURE 9-8 Ultrasonograms of the pancreas showing an islet beta-cell tumor (arrows) in a 13-year-old Borzoi (**A**) and a 14-year-old Miniature Poodle (**B**). **C**, Ultrasonogram of the peripancreatic tissue showing a metastatic beta-cell tumor (arrows) in a 5-year-old Golden Retriever.

tumors in dogs. In a series of 14 dogs with insulinoma, the sensitivity of conventional pre- and postcontrast CT for detection of insulinoma and lymph node metastasis was 71% and 40%, respectively (Robben et al, 2005). Unfortunately, CT also identified 28 false-positive lesions in lymph nodes. Conventional pre- and postcontrast CT has been replaced by dual-phase computed tomographic angiography (CTA) for the identification and localization of insulinomas and metastases in humans (Chatziioannou et al, 2001). Dual phase CTA techniques have been developed in dogs and preliminary studies in dogs with insulinoma have been promising (Caceres et al, 2006; Iseri et al, 2007; Mai and Caceres, 2008). During dual-phase CTA, images are acquired during the arterial and venous phases after IV injection of contrast medium. Most human insulinomas are histopathologically hypervascular, and the CT images obtained during the arterial phase may clearly delineate enhancing tumor lesions (Gritzmann et al, 2004). Insulinomas in dogs are also assumed to be hypervascular. A study evaluating dual-phase CTA of the pancreas in 10 healthy Beagle dogs identified an arterial phase peak at 15 ± 2 seconds after contrast medium injection followed by a venous phase peak where the pancreatic parenchyma was clearly delineated at 28 ± 9 seconds and appearance of the equilibrium phase approximately 70 seconds after injection (Fig. 9-9; Iseri et al, 2007). Caceres, et al., (2006) identified a purely arterial pancreatic window of 5 to 6 seconds after contrast administration in nine healthy Beagles. Evaluation of a dog with insulinoma revealed a hyperattenuating mass at the arterial phase of the dual-phase CTA, and the size and location of the tumor observed on the CT images were consistent with those seen at surgery (Iseri et al, 2007).

In a subsequent study involving three dogs with insulinoma, dual-phase CTA identified lesions not seen on ultrasonography, including the primary insulinoma in two dogs (Mai and Caceres, 2008). Findings with dual-phase CTA were in agreement with the surgical findings in all three dogs. In two dogs, the insulinomas had marked contrast enhancement during the arterial phase of the study with less enhancement during the venous phase and was isoattenuating to the rest of the pancreas during the delayed phase of the study. In the third dog, a metastasized lymph node but not the pancreatic insulinoma had strong enhancement at the arterial phase comparable to that seen in the primary insulinoma in the other two dogs. Lack of arterial enhancement of an insulinoma has been reported in humans with up to 45% of pancreatic insulinomas being hypo- to isoattenuating to the rest of the pancreas during the arterial phase (Van Hoe et al, 1995). Occasionally the tumor is hyperattenuating at the venous but not the arterial phase of the study. Evaluation of the arterial and venous phase of a contrast-enhanced CT is currently recommended immediately prior to surgery to identify the location of the primary insulinoma and its metastatic sites. The decision to either pursue surgery with medical treatment to follow, or cancel surgery and initiate medical treatment will be dependent, in part, on the findings of the CT study.

Scintigraphy

Somatostatin receptor scintigraphy using the radiopharmaceutical drug indium (In)-111 pentetreotide has been used to image pancreatic islet cell tumors in humans (Kvols et al, 1993; Lamberts et al, 1993). In humans, localization of beta-cell tumors with somatostatin receptor scintigraphy has been inconsistent and of limited value (Lamberts et al, 1991; Buetow et al, 1997). Positive and negative scan results have been correlated with the

presence or absence of somatostatin receptors in tumor biopsy samples. Five somatostatin receptor subtypes, designated sst1 to sst5, are recognized in human tissue (Reubi et al, 2001). One variable influencing the success of somatostatin receptor scintigraphy is the predominant somatostatin receptor subtype expressed by the insulinoma, which dictates its affinity for pentetreotide. Ligand binding studies on beta-cell tumors in humans have identified different subtypes of somatostatin receptors, with variable binding capacities for somatostatin and somatostatin analogs, which may explain the variability of results (Lamberts et al, 1991; Bruns et al, 1994).

In the dog, the predominant somatostatin receptor containing high-affinity binding sites for the somatostatin analog octreotide and the radiopharmaceutical In-111 pentetreotide in insulin-secreting tumors has been sst2 (Robben et al, 1997; Garden et al, 2005). Somatostatin receptor scintigraphy using radio-labeled

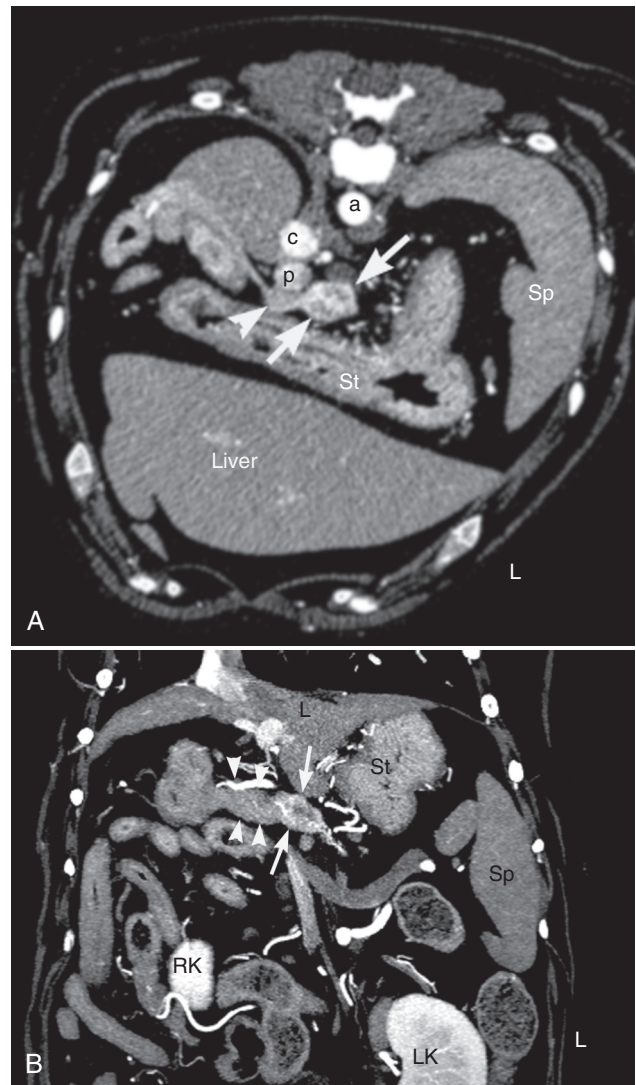


FIGURE 9-9 Transverse (A) computed tomography (CT) image and a maximum intensity projection CT image in the dorsal plane (B) of a pancreatic beta-cell tumor obtained during the arterial phase of dual-phase CT angiography in a dog that presented with severe hypoglycemia and inappropriate hyperinsulinemia. Note the marked distinction between the beta-cell tumor (arrows) and the remaining normal pancreas (arrow heads). (Images courtesy of Dr. Eric Johnson.) a, aorta; c, caudal vena cava; p, portal vein; St, stomach; Sp, spleen; RK and LK, right and left kidney.

octreotide or In-111 pentetreotide was used to identify beta-cell neoplasia in seven dogs with inconclusive findings on abdominal ultrasonography (Robben et al, 1997; Lester et al, 1999). Somatostatin receptor scintigraphy was effective in identifying the primary insulin-secreting tumor in five of seven dogs and larger metastases in the regional lymph nodes and liver in three of three dogs and two of three dogs, respectively. Small metastases in the liver were not detected in one dog. In a subsequent study by Garden, et al., (2005) using In-111 pentetreotide, scintigraphic scans in four of five dogs with insulinoma showed that abnormal foci of In-111 pentetreotide activity attributed to the insulinoma but the anatomic location of the tumors was correctly predicted in only one of these dogs. The scan in the fifth dog was equivocal; a 1.5 cm insulinoma was identified in the distal left limb of the pancreas at surgery. In a series of 14 dogs with insulinoma, the sensitivity of single-photon emission CT using radiolabeled octreotide was 43% and lymph node metastasis was identified in none of five dogs (Robben et al, 2005). Negative scan results could reflect the expression of somatostatin receptors with low affinity for pentetreotide, low expression density of sst2 receptors, or small size of the tumor, rather than absence of the tumor itself (Garden et al, 2005).

Somatostatin receptor scintigraphy offers intriguing options for identifying insulin-secreting tumors and determining potential responsiveness of the tumor to octreotide therapy. Presumably, positive scintigraphic scans would also predict a positive response to treatment with the somatostatin analog octreotide (see Somatostatin Therapy).

TREATMENT OF BETA-CELL NEOPLASIA

Surgical Versus Medical Therapy

Treatment options for a beta-cell tumor include surgical exploration, medical treatment for chronic hypoglycemia, or both. Surgery offers a chance to cure dogs with a resectable solitary mass. In dogs with nonresectable tumors or with obvious metastatic lesions, removal or “debulking” of as much abnormal tissue as possible frequently results in remission, or at least alleviation, of clinical signs and an improved response to medical treatment. Survival time is longer in dogs that undergo surgical exploration and tumor debulking followed by medical therapy, compared with dogs only treated medically (Tobin et al, 1999). Despite these benefits, surgery remains a relatively aggressive mode of diagnosis and treatment, in part because of the high prevalence of metastatic disease, the older age of many dogs at the time beta-cell neoplasia is diagnosed, the potential for postoperative pancreatitis, and the unpredictable response to surgery as it relates to improvement in hypoglycemia and clinical signs. As a general rule, we are less aggressive about recommending surgery in aged dogs (i.e., older than 12 years of age), dogs with extensive metastatic disease identified by diagnostic imaging, and dogs with concurrent disease that significantly enhances the anesthetic risk.

Medical management of chronic hypoglycemia should be initiated when an exploratory celiotomy is not performed or when metastatic or inoperable neoplasia results in recurrence of clinical signs. Medical therapy revolves around nonspecific antihormonal therapy designed to increase the blood glucose concentration and decrease the occurrence of clinical signs. Many dogs with metastatic disease can be managed medically for several months to more than a year. Medical therapy, however, has no potential for providing a “cure” or for preventing metastasis of malignant beta-cell neoplasia.

Perioperative Management of Dogs Undergoing Surgery

The intent of surgery should be to remove as much abnormal tissue as possible, including resectable sites of metastases. The success of surgery depends in part on providing appropriate fluid therapy, dextrose, and supportive care during the perioperative period to avoid severe hypoglycemia and postoperative pancreatitis and to improve the likelihood of an uneventful recovery. Euthanasia is not recommended regardless of the findings at surgery. Many dogs with metastatic disease can be managed medically for several months to more than a year.

Until surgery is performed, the dog should be protected from episodes of severe hypoglycemia. This can usually be accomplished through frequent feeding of small meals and administration of glucocorticoids (Box 9-7). A continuous IV infusion of a balanced

BOX 9-7 Long-Term Medical Therapy for Dogs with a Beta-Cell Tumor

Standard Treatments

1. Dietary therapy
 - a. Feed canned or dry food in three to six small meals daily.
 - b. Dietary fat, complex carbohydrates, and fiber help prolong postprandial glucose absorption.
 - c. Avoid foods containing monosaccharides, disaccharides, propylene glycol, and corn syrup.
2. Limit exercise to walks; avoid strenuous exercise.
3. Glucocorticoid therapy
 - a. Prednisone, 0.5 mg/kg divided into two doses initially.
 - b. Gradually increase dose and frequency of administration, as needed.
 - c. Goal is to control clinical signs, not to reestablish euglycemia.
 - d. Consider alternative treatments if signs of iatrogenic hypercortisolism become severe or glucocorticoids become ineffective.

Additional Treatments

1. Diazoxide therapy
 - a. Continue standard treatment; reduce glucocorticoid dose if polyuria and polydipsia is unacceptable.
 - b. May initiate diazoxide early when glucocorticoid dose is low, or later when glucocorticoids become ineffective or polyuria and polydipsia becomes unacceptable.
 - c. Diazoxide, 5 mg/kg every 12 hours initially.
 - d. Gradually increase dose as needed, not to exceed 60 mg/kg/day.
 - e. Goal is to control clinical signs, not to reestablish euglycemia.
2. Somatostatin therapy
 - a. Continue standard treatment; reduce glucocorticoid dose if polyuria and polydipsia is unacceptable.
 - b. Octreotide (Sandostatin), 10 to 40 µg/dog administered subcutaneously every 12 hours to every 8 hours.
3. Streptozotocin therapy
 - a. Effectiveness in improving hypoglycemia, controlling clinical signs, and prolonging survival is variable and potentially severe adverse reactions are common (see Streptozotocin).
 - b. Continue standard treatment; reduce glucocorticoid dose if polyuria and polydipsia is unacceptable.
 - c. 0.9% saline diuresis for 3 hours, then streptozotocin, 500 mg/m², in 0.9% saline and administered intravenously over 2 hours, then 0.9% saline diuresis for 2 additional hours.
 - d. Administer antiemetics immediately after streptozotocin administration to minimize vomiting.
 - e. Repeat treatment every 3 weeks until hypoglycemia resolves or adverse reactions develop (e.g., pancreatitis, renal failure).

electrolyte solution containing 2.5% to 5% dextrose before, during, and immediately after surgery is important. Although this does not restore euglycemia, these solutions provide a substrate for CNS function, thereby minimizing CNS signs in most dogs. Concentrations of dextrose in excess of 5% should be avoided to prevent overstimulation of the pancreatic tumor and rebound, sometimes fatal, hypoglycemia. The IV dextrose infusion can be initiated the evening before surgery, at the time food and water are withheld, and continued throughout the perioperative period. Initiation of fluid therapy before surgery also helps ensure adequate circulation to the pancreas, thereby minimizing the risk of postoperative pancreatitis. The goal of the dextrose infusion is to prevent clinical signs of hypoglycemia and to maintain the blood glucose concentration at greater than 40 mg/dL (2.2 mmol/L), not to reestablish a normal blood glucose concentration. If the dextrose infusion is ineffective at preventing severe hypoglycemia during the perioperative period, a constant-rate infusion of glucagon should be considered (see Medical Therapy for an Acute Hypoglycemic Crisis). Glucagon is a potent stimulant of hepatic gluconeogenesis and is effective in maintaining normal blood glucose concentrations in dogs with an insulin-secreting tumor when administered by constant-rate infusion.

Intraoperative Considerations

Attention to the patient's blood glucose concentration and maintenance of adequate fluid therapy during surgery are imperative for the dog with beta-cell neoplasia. In a recent study, the addition of medetomidine (5 µg/kg IM) to the preanesthetic medication protocol significantly decreased plasma insulin concentrations, increased plasma glucose concentrations, and decreased the intraoperative glucose administration rate in 12 dogs undergoing surgery for beta-cell tumor, compared with 13 dogs that did not receive medetomidine prior to surgery (Guedes and Rude, 2013). These findings support the judicious use of medetomidine at low doses as an adjunct to the anesthetic management of dogs with beta-cell neoplasia.

Monitoring the blood glucose concentration every 30 to 60 minutes during surgery using a point-of-care or PBGM device allows objective assessment of the dog's blood glucose status. The goal is to maintain the blood glucose concentration greater than 40 mg/dL (2.2 mmol/L), not to establish a normal blood glucose concentration per se. Moderate changes in the blood glucose concentration can be monitored and adjustments made in the rate of IV dextrose administration, as needed, to prevent the

development of severe hypoglycemia (i.e., a blood glucose concentration < 40 mg/dL). Fortunately, it is uncommon for a dog in stable condition with a beta-cell tumor to require more than a 5% dextrose solution given intravenously during surgery. This infusion usually maintains the blood glucose concentration above 40 mg/dL. If a 5% dextrose infusion is ineffective in preventing severe hypoglycemia during surgery, a constant-rate infusion of glucagon should be considered (see Medical Therapy for an Acute Hypoglycemic Crisis).

Adequate fluid therapy just prior to, during, and immediately after surgery is extremely important for minimizing the development of pancreatitis. Digital manipulation and dissection of the pancreas cause inflammation. The severity of inflammation depends on the gentleness of the palpation, circulation to the pancreas, and surgical procedures performed. Providing adequate fluid therapy prior to and during surgery ensures that every means of maintaining circulation through the microvasculature of the pancreas has been used and helps minimize the development of pancreatitis. We routinely administer fluids at a rate of 60 to 100 mL/kg/24 hr during surgery and for 24 to 72 hours after the procedure, unless concurrent problems (e.g., heart failure, hypoproteinemia) are present that may affect the dog's ability to handle IV fluids.

During surgery, as much of the pancreas as possible should be examined visually. A complete, gentle digital inspection of this organ should then be undertaken. The importance of gentle handling of the pancreas cannot be overemphasized; failure to handle the organ gently may result in severe, potentially life-threatening pancreatitis. A thorough examination of the liver, surrounding lymph nodes, and omentum for metastatic sites should also be done.

Frequency of Tumor Identification. Most dogs with insulin-secreting tumors have masses that are easily visible to the surgeon inspecting the pancreas (Fig. 9-10). In a minority of dogs, the tumor is not visible but can be palpated during gentle but thorough digital examination of the pancreas. Multiple pancreatic masses may also occur. Ninety-nine (88%) of 111 dogs with insulin-secreting tumors at UC Davis had an obvious mass in the pancreas at the time of surgery.

Tumor Location. There is no predisposition for tumor location in the pancreas (Fig. 9-11). In our 99 dogs in which a mass was identified in the pancreas, the mass was located in the right (duodenal) limb of the pancreas in approximately 41%, in the left (splenic) limb of the pancreas in 40%, and in the central region

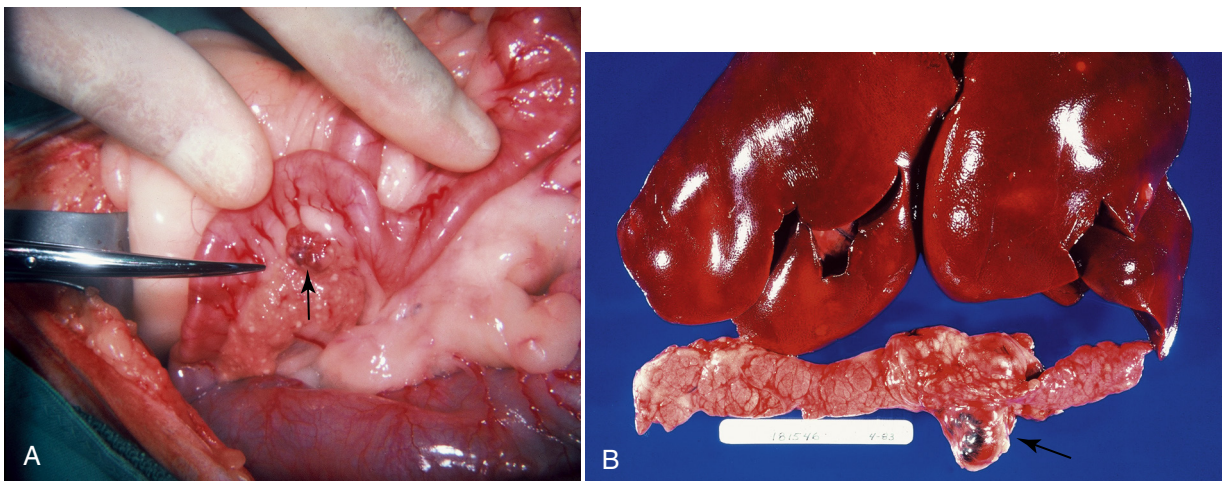


FIGURE 9-10 A and B, Photographs of pancreatic insulin-secreting islet beta-cell tumors (arrows).

(body) of the pancreas in 19%. In five of the remaining 12 dogs, a diffuse, microscopic islet cell carcinoma was recognized histologically in an arbitrarily resected portion of the right limb of the pancreas. Diffuse thickening of the pancreas was evident on digital palpation of the pancreas at the time of surgery in three of these five dogs; the pancreas was visually and digitally normal in two dogs. In three dogs, there was no visible mass and no metastatic sites, the pancreas was normal on digital palpation, and histologic examination of a portion of the right limb of the pancreas failed to identify an insulin-secreting tumor. One year later a pancreatic mass subsequently confirmed as an insulinoma was identified in one of the dogs. In two dogs, there was no visible mass and no metastatic sites, the pancreas was normal on digital palpation, and histologic examination of a portion of the right limb of the pancreas failed to identify an insulin-secreting tumor but subjectively there was marked increase in the number of islets and “islands” of beta cells scattered throughout the pancreas. Periodic evaluations of the dogs identified persistent hypoglycemia and hyperinsulinemia but failed to identify a pancreatic mass. One dog was lost to follow-up at 18 months after surgery and a necropsy was performed on the other dog approximately 5 years after surgery; histologic changes suggestive of “beta cell hyperplasia” were still evident, and a pancreatic mass was not identified. Enlargement of a mesenteric lymph node adjacent to the pancreas was evident in two dogs, but a mass was not identified in the pancreas per se. Histologic examination of the excised lymph node confirmed metastatic beta-cell tumor. Hyperinsulinism and hypoglycemia persisted in both dogs after surgery.

Tumor location has important ramifications for the success of surgery. In general, solitary tumors in the left or right limb of the pancreas are readily excisable with minimal damage to the pancreas and a low prevalence of postoperative pancreatitis. In contrast, tumors in the body of the pancreas are often intimately intertwined with the pancreatic ducts, blood vessels, and lymphatics. Surgical removal often requires extensive manipulation and dissection of the pancreas. Severe and potentially life-threatening pancreatitis that requires aggressive and often extended treatment is a common postoperative complication despite appropriate perioperative treatment aimed at preventing its development. In addition, complete excision of the tumor is almost impossible

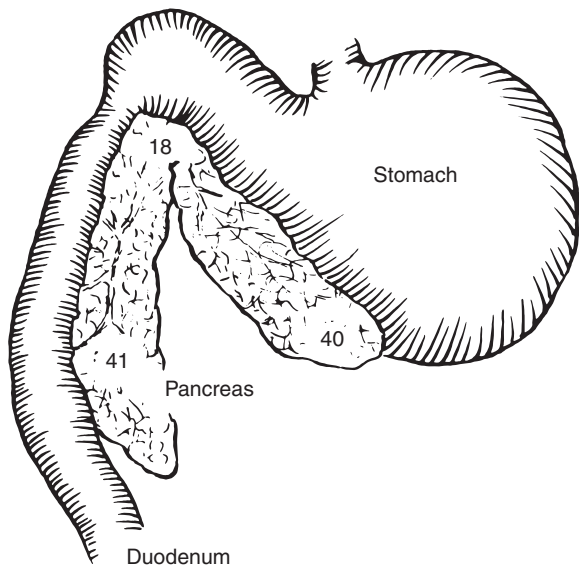


FIGURE 9-11 Diagram of tumor location in the pancreas in 99 dogs with an insulin-secreting islet beta-cell tumor.

and hypoglycemia typically recurs shortly after surgery. Prior to surgery we routinely discuss with the client the possible locations of the tumor and the implications that location has on attaining a successful outcome. We strongly recommend against tumor removal if the insulin-secreting tumor is located in the body of the pancreas because of the high probability of life-threatening postoperative complications. We inform the client that there is a one in five chance of the dog having inoperable disease and that if such disease is found, we advise closing the abdomen and treating the dog medically rather than risk the development of severe pancreatitis by trying to remove the tumor.

Failure to Identify a Mass: Use of Methylene Blue. IV methylene blue infusion has been advocated for intraoperative identification of a beta-cell tumor in the dog (Fingeroth and Smeak, 1988; Fingeroth et al, 1988). Methylene blue is an azo dye that, when administered intravenously, is concentrated in the parathyroid glands and endocrine pancreas. Methylene blue intensely stains hyperfunctional, adenomatous, or carcinomatous areas of these organs. Normal pancreatic endocrine tissue is stained a dusky slate blue, whereas hyperfunctioning tissue is stained more intensely, often a reddish blue. In one dog, methylene blue also successfully identified an ectopic islet cell tumor and differentiated metastatic from nonmetastatic nodules in surrounding tissue (Smeak et al, 1988).

Methylene blue is administered as an IV infusion by mixing appropriate volumes of methylene blue in 250 mL of normal isotonic saline solution to obtain a total dose of 3 mg methylene blue per kilogram of body weight (Fingeroth and Smeak, 1988). The entire solution is given over a period of 30 to 40 minutes. Maximal staining of the endocrine pancreas occurs approximately 30 minutes after initiation of the infusion. Complications with methylene blue infusion include Heinz body hemolytic anemia, acute kidney failure, pseudo-cyanosis (i.e., blue-appearing oral mucous membranes), green-tinged urine, and possibly pancreatitis. Hemolytic anemia is common, with the hematocrit declining to less than 25% 2 to 3 days after surgery.

We do not routinely use methylene blue because of its postoperative complications, the routine use of dual-phase CTA prior to surgery, and the ability to grossly identify abnormal tissue in the vast majority of our dogs with beta-cell neoplasia. If our surgeon fails to recognize a mass and the diagnosis has been confirmed by glucose and insulin measurements, the recommendation is to remove the right or left limb of the pancreas in the hope of removing the portion that contains the tumor. In theory, 90% of the pancreas could be removed without causing overt diabetes mellitus or exocrine pancreatic insufficiency.

Sites of Metastasis. Little correlation appears to exist between tumor size or shape and its malignant potential. A complete inspection of the abdominal contents is imperative to identify unsuspected abnormalities as well as sites of metastasis. The most common sites of tumor spread include the regional lymphatics and lymph nodes (duodenal, mesenteric, hepatic, splenic), the liver, and the peripancreatic omentum. Failure to identify metastatic disease is common during surgery. A solitary pancreatic mass is commonly removed in toto, with the belief that the dog has been “cured,” only to have clinical signs of hyperinsulinism recur weeks to months later. In our experience, almost all beta-cell tumors in the dog are malignant. Unfortunately, initial clinical signs are often vague and not worrisome to the owner; weeks to months may elapse between the onset of clinical signs and establishment of the diagnosis, and as a result, the likelihood of metastasis at the time of exploratory surgery is high.

Recommendations if Metastasis Is Identified. Ideally, all abnormal-appearing tissue should be removed, if possible, and

submitted for histologic evaluation. When abnormal tissue cannot be entirely removed, debulking of the tumor mass may be beneficial. Biopsy of suspected tumor tissue is the least a surgeon should accomplish. The surgeon must always weigh the potential gains obtained with aggressive tumor removal and debulking against the potential complications that may develop as a result of the surgical procedure. This is especially important when dealing with the pancreas, because life-threatening pancreatitis can develop after extensive manipulation and dissection of the gland. Because medical treatment is a viable option after surgery, euthanasia at the time of surgery and heroic attempts to remove all abnormal tissue are not recommended in a dog with metastatic disease, especially if the latter course increases the risk of postoperative complications.

Postoperative Complications. The most common postoperative complications are pancreatitis, hyperglycemia, and hypoglycemia. The development of these complications is directly related to the expertise of the surgeon in handling the pancreas and excising these tumors, the location of the tumor in the pancreas (i.e., peripheral limb versus body), the presence or absence of functional metastases, and the adequacy of fluid therapy during the perioperative period.

Pancreatitis. IV administration of polyionic fluids with 2.5% to 5% dextrose (60 to 100 mL/kg/24 hr) and nothing by mouth prior to, during, and for 24 to 48 hours after surgery, followed by appropriate dietary therapy during the ensuing week, is helpful in minimizing the development of pancreatitis. We rely on physical examination findings in determining when to initiate oral water and a bland diet. Circulating pancreatic enzyme concentrations (e.g., canine pancreatic-specific lipase [cPL]) are usually not determined after surgery. Arbitrarily treating the dog for pancreatitis without determining the serum pancreatic enzyme concentrations beforehand has produced excellent results. Despite gentle handling of the pancreas during surgery, aggressive fluid therapy during the perioperative period, and appropriate dietary therapy during the postoperative period, nine (13%) of 70 dogs undergoing surgery for beta-cell tumor at UC Davis still developed clinical signs of acute pancreatitis. Three of the nine dogs died as a result of pancreatitis; the tumor was located in the body of the pancreas and was difficult to excise in all three dogs.

Diabetes Mellitus. Occasionally dogs develop transient diabetes mellitus after surgical removal of an insulin-secreting tumor. Diabetes mellitus is believed to result from inadequate insulin secretion by “atrophied” normal beta cells. Removal of all or a majority of the neoplastic cells acutely deprives the animal of insulin. Until the normal beta cells regain their secretory capability, the dog is hypoinsulinemic and may require exogenous insulin injections to maintain euglycemia. It was once thought that postsurgical hyperglycemia and glycosuria were excellent prognostic signs indicating total removal of insulin-secreting neoplastic cells. However, most of our dogs have required exogenous insulin only transiently after surgery and ultimately have required medical management for an exacerbation of an insulin-secreting tumor several weeks to months after their need for insulin therapy dissipates.

Postsurgical insulin therapy is initiated only when hyperglycemia and glycosuria persist for 1 to 2 days after discontinuation of all dextrose-containing IV fluids. Initial insulin therapy should be conservative—that is, 0.25 U of Lente or neutral protamine Hagedorn (NPH) insulin per kilogram of body weight given once daily. Subsequent adjustments in dosage or frequency of administration should be based on clinical response and blood glucose determinations (see Chapter 6).

The need for insulin treatment is usually transient, lasting from a few days to a few months. Most of these dogs still have

neoplastic beta cells in the pancreas, liver, lymph nodes, or peripancreatic tissues that multiply and eventually reach a population density capable of secreting enough insulin to cause hypoglycemic signs to recur. For these dogs, resolution of diabetes is followed by a variable period of euglycemia, which eventually progresses to hypoglycemia. Owner evaluation of the pet’s urine glucose is helpful in identifying when insulin therapy is no longer needed. Persistently negative urine glucose in conjunction with cessation of polyuria and polydipsia is an indication to discontinue insulin therapy. If hyperglycemia and glycosuria recur, insulin therapy can be reinstated, but at a lower insulin dosage. The development of permanent insulin-requiring diabetes mellitus after surgical removal of a solitary insulin-secreting tumor is uncommon and implies additional abnormalities involving the beta cells (e.g., beta-cell degeneration, islet hypoplasia; see Chapter 6). Permanent diabetes mellitus has developed in only two of the dogs that underwent surgical removal of an insulin-secreting tumor at our hospital. Both dogs were lost to follow-up after 1 to 2 years, and at that time both dogs were still receiving insulin injections twice a day to control hyperglycemia.

Persistent Postoperative Hypoglycemia. Dogs that remain hypoglycemic after surgical removal of an insulin-secreting tumor have functional metastatic disease. Medical therapy should be initiated in dogs with persistent postoperative hypoglycemia. During the initial 48 to 72 postoperative hours, IV infusion of 2.5% to 5% dextrose should be continued. The goal is to prevent clinical signs of hypoglycemia (especially seizures), not to reestablish a normal blood glucose concentration. Additional therapy may be needed if hypoglycemic seizures occur (Box 9-8; also see Medical Therapy for an Acute Hypoglycemic Crisis). Small meals should be fed every 4 to 6 hours, beginning as soon after surgery as possible. A diet acceptable for the treatment of pancreatitis should be fed initially. Additional therapy may be needed, depending on the efficacy of the frequent feedings in maintaining remission of clinical hypoglycemia (see Medical Therapy for Chronic Hypoglycemia). If a dog becomes symptomatic despite the frequent feedings, medical therapy should be attempted before euthanasia is recommended.

BOX 9-8 Medical Therapy for Hypoglycemic Seizures Caused by an Insulin-Secreting Beta-Cell Tumor

Seizures at Home

- Step 1: Rub sugar solution on pet’s buccal mucosa.
- Step 2: Once pet is sternal, feed a small meal.
- Step 3: Call the veterinarian.

Seizures in Hospital

- Step 1: Administer 1 to 5 mL (depending on dog size) of 50% dextrose (diluted) intravenously slowly over 1 to 2 minutes followed by continuous IV infusion of 5% dextrose in water (i.e., D5W).
- Step 2: Once animal is sternal, feed a small meal.
- Step 3: Initiate long-term medical therapy (see Box 9-7).

Intractable Seizures in Hospital

- Step 1: Administer 2.5% to 5% dextrose in water intravenously at 1.5 to 2 times maintenance fluid rate.
- Step 2: Add 0.5 to 1 mg of dexamethasone/kg to IV fluids and administer over 6 hours; repeat every 12 to 24 hours, as necessary.
- Step 3: If above fails, administer glucagon USP (Eli Lilly) intravenously by constant rate infusion at an initial dosage of 5 to 10 ng/kg/min.
- Step 4: If necessary, control seizure activity with diazepam or phenobarbital until medical treatment becomes effective in controlling hypoglycemia.

Evaluating the Long-Term Success of Surgery: Is the Dog Cured?

The long-term success of surgery can be difficult to predict in dogs with a “solitary” mass that is removed in toto and subsequent blood glucose concentration returns to normal. The most efficient and logical initial method for evaluating these patients for recurrence of beta-cell neoplasia is periodic measurement (i.e., every month initially) of a fasting blood glucose concentration. The fasting blood glucose concentration should be consistently greater than 70 mg/dL (3.9 mmol/L) if beta-cell neoplasia has not recurred. Recurrence of beta-cell neoplasia should be suspected if the blood glucose concentration is less than 70 mg/dL. Confirmation of recurrence requires measurement of the serum insulin concentration when the blood glucose concentration is less than 60 mg/dL (see Confirming the Diagnosis of an Insulin-Secreting Beta-Cell Tumor: Serum Insulin Determination).

Medical Therapy for an Acute Hypoglycemic Crisis

The acute onset of clinical signs caused by hypoglycemia typically occurs at home after exercise or consumption of food that is easily digestible and rapidly absorbed; during the immediate postoperative period in the dog with functioning metastases or inoperable neoplasia; or as a result of inadvertently aggressive IV dextrose administration at the time hypoglycemia is initially identified. Therapy depends on the severity of clinical signs and the location of the dog (i.e., home versus hospital) and initially involves administration of glucose, either as food or sugar solution by mouth or as an IV dextrose solution.

If an owner contacts a veterinarian by telephone and reports that the pet is having a hypoglycemic seizure, we do not recommend transporting the dog to a veterinary hospital. Rather, the owner should be instructed to rub a sugar solution on the pet’s buccal mucosa. Hypoglycemic dogs usually respond in 1 to 2 minutes. The owner should be instructed to never place fingers in, or pour the sugar solution down, the pet’s mouth. Once the dog or cat is sternal and cognizant of its surroundings, it should be fed a small meal and brought to the veterinarian.

At home subcutaneous administration of glucagon is used to treat severe hypoglycemia in human diabetics. Glucagon quickly

increases blood glucose through stimulation of hepatic glycogenolysis and gluconeogenesis. In a recent study, subcutaneous administration of glucagon resulted in a rapid and significant increase in serum glucose concentrations in healthy Beagles but the effect was short-lived (Zeugswetter et al, 2012; Fig. 9-12). Although clinical trials are needed, at home glucagon emergency kits used to treat severe hypoglycemia in human diabetics may become a viable option for the short-term treatment of severe hypoglycemia in dogs or cats and provide the time needed to get the dog or cat to an emergency veterinary hospital for care (Niessen, 2012).

In the hospital, clinical signs of hypoglycemia can usually be alleviated initially with IV administration of 50% dextrose, diluted, followed by continuous IV infusion of 5% dextrose (i.e., dextrose 5% in water [D5W]). In dogs with beta cell neoplasia, dextrose should be administered in small amounts slowly (e.g., 1 to 5 mL increments depending on the size of the dog over a period of 1 to 2 minutes) to effect. Rapid administration of large boluses of glucose to a dog with suspected or proven beta cell neoplasia can result in severe rebound hypoglycemia caused by excessive insulin secretion by the tumor in response to the rapid increase in the blood glucose concentration. The goal of therapy is to control neurologic signs (primarily seizures), not correct hypoglycemia. Once neurologic signs have been controlled with judicious IV administration of dextrose, frequent feedings and glucocorticoids can be initiated (see Box 9-7).

If the dextrose infusion is ineffective in preventing severe hypoglycemia or breaking the cycle of hypoglycemia and hyperglycemia, a constant-rate infusion of glucagon should be considered. Glucagon is a potent stimulant of hepatic glycogenolysis and gluconeogenesis and is effective in maintaining normal blood glucose concentrations in dogs with beta-cell neoplasia when administered by constant-rate infusion (Fischer et al, 2000; Fig. 9-13). One milligram of lyophilized glucagon USP (Eli Lilly) is reconstituted with the diluent provided by the manufacturer, and the solution is added to 1 L of 0.9% saline, making a 1 µg/mL solution, which can be administered by syringe pump. The initial dosage is 5 to 10 ng per kilogram of body weight per minute. The dosage is adjusted as needed to maintain the blood glucose concentration between 60 and 100 mg/dL (3.4 and 5.6 mmol/L). When discontinuing

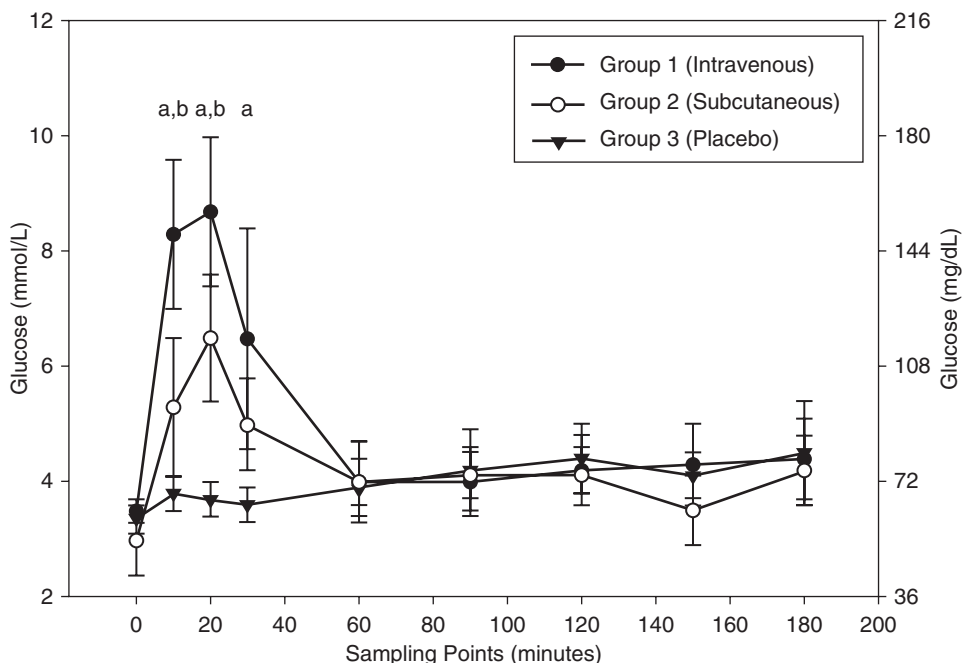


FIGURE 9-12 Mean glucose concentrations (mmol/L and mg/dL) over 180 minutes after the subcutaneous (SC) and intravenous (IV) injection of synthetic glucagon or 0.9% saline solution (placebo). (From Zeugswetter FK, et al.: Metabolic and hormonal responses to subcutaneous glucagon in healthy beagles, *J Vet Emer Crit Care* 22:558, 2012.) Bars indicate standard deviations. *a*, Significant difference of SC versus placebo injection; *b*, significant difference of SC versus IV injection; $P < 0.05$ is considered significant.

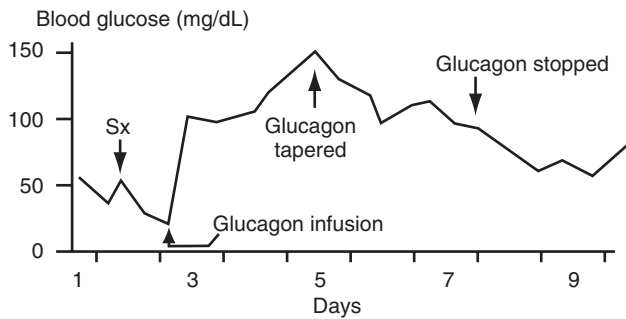


FIGURE 9-13 Blood glucose concentrations in a 13-year-old female spayed Pomeranian before and after surgical removal of an insulin-secreting islet beta-cell tumor. Pancreatitis and severe hypoglycemia developed postoperatively. The hypoglycemia resolved, and euglycemia was maintained after initiation of a constant-rate intravenous (IV) infusion of glucagon. The dosage of glucagon was gradually tapered beginning on day 5, feeding of small amounts of food was begun on day 7, and the IV glucagon infusion was stopped on day 8. Severe hypoglycemia did not recur. Sx, Surgery.

glucagon, the dose should be gradually decreased over 1 to 2 days and the blood glucose concentration monitored for recurrence of severe hypoglycemia.

Occasionally, a hypoglycemic dog with CNS signs fails to respond to glucose or glucagon administration. These signs could be the result of a disorder unrelated to hypoglycemia. However, irreversible cerebral lesions may result from long-term, severe hypoglycemia and the resultant cerebral hypoxia. Cerebral hypoxia predisposes the nervous tissue to edema, causing increased CSF pressure and cell death. These animals have a guarded to grave prognosis. Therapy is directed at providing a continuous supply of glucose as a 5% solution given intravenously or by stimulating hepatic glucose production with a constant-rate infusion of glucagon. Simultaneously, seizure activity is controlled with diazepam or stronger anticonvulsant medication (e.g., phenobarbital). Last, if cerebral edema is suspected, treatment with mannitol, furosemide, and/or dexamethasone should be considered (Fenner, 1995).

Medical Therapy for Chronic Hypoglycemia

See [Box 9-7](#).

Background

Medical management for chronic hypoglycemia should be initiated when an exploratory celiotomy is not performed or when metastatic or inoperable neoplasia results in recurrence of clinical signs. The goals of medical therapy are to reduce the frequency and severity of clinical signs and to avoid an acute hypoglycemic crisis, not to establish euglycemia per se. Medical therapy typically involves nonspecific antihormonal therapy. Antihormonal therapy is palliative and should minimize hypoglycemia by providing a continuous source of glucose from the gastrointestinal tract (frequent feedings), increasing hepatic glycogenolysis and gluconeogenesis (glucocorticoids), or inhibiting the synthesis, secretion, or peripheral cellular actions of insulin (glucocorticoids, diazoxide, somatostatin). Antihormonal therapy consists primarily of frequent feedings and glucocorticoids (see [Box 9-7](#)). Surgical debulking of functional masses may enhance the effectiveness of medical therapy. The best results are obtained when surgical debulking is performed shortly after the diagnosis of an insulin-secreting tumor has been established, although we have had a few

dogs benefit from surgical debulking after medical treatment has become ineffective in controlling clinical signs of hypoglycemia. One of our dogs underwent surgical debulking on three separate occasions; the dog survived 3 years before succumbing to metastatic disease involving the lungs.

Alloxan and streptozotocin are drugs with specific toxicity directed at beta cells. The potential for serious adverse reactions has limited the use of these drugs for the treatment of insulin-secreting tumors in dogs. However, a viable treatment protocol using streptozotocin in dogs has been described, and studies to determine its value in the treatment of insulin-secreting tumors have been reported (Moore et al, 2002; Northrup et al, 2013).

Frequent Feedings

Dogs with insulin-secreting tumors have a persistent absolute or relative excess of circulating insulin. Frequent feedings provide a constant source of calories as a substrate for the excess insulin secreted by the tumor and help to reduce the frequency of hypoglycemic episodes. Diets high in fat, complex carbohydrates, and fiber delay gastric emptying, slow intestinal glucose absorption, and help minimize a rapid increase in the portal blood glucose concentration that could stimulate excessive pancreatic insulin secretion. Simple sugars are rapidly absorbed, have a potent stimulatory effect on insulin secretion by neoplastic beta cells, and should be avoided. A combination of canned and dry food, fed in three to six small meals daily, is recommended. Daily caloric intake should be controlled because hyperinsulinemia promotes obesity. Exercise should be limited to walks on a leash.

Glucocorticoid Therapy

Glucocorticoid therapy should be initiated when dietary manipulations are no longer effective in preventing clinical signs of hypoglycemia. Glucocorticoids antagonize the effects of insulin at the cellular level, stimulate hepatic glycogenolysis, and indirectly provide the necessary substrates for hepatic gluconeogenesis. Prednisone (dog) or prednisolone (cat) are the glucocorticoids most often used. The initial dosage is 0.25 mg/kg by mouth every 12 hours. Adjustments in the dose are based on clinical response. The dose of prednisone required to control clinical signs increases with time in response to growth of the tumor and its metastatic sites. Eventually, the adverse effects of prednisone, specifically polyuria and polydipsia, become unacceptable to clients. This typically occurs when the prednisone dosage approaches 1 mg/kg twice daily, although there is dog to dog variability in development of adverse effects and owner tolerance of the adverse effects. When adverse effects become intolerable, the dose of prednisone should be reduced by 25% to 50% (not stopped) and additional therapy considered.

Diazoxide Therapy

Diazoxide (Proglycem) is a benzothiadiazide diuretic that inhibits insulin secretion, stimulates hepatic gluconeogenesis and glycogenolysis, and inhibits tissue use of glucose. The net effect is the development of hyperglycemia. Diazoxide does not inhibit insulin synthesis and does not have cytotoxic (antineoplastic) effects. Diazoxide therapy can be initiated early in the medical treatment of a beta-cell tumor when the glucocorticoid dose is low and polyuria and polydipsia are acceptable to the client or can be initiated later when glucocorticoids are no longer effective in controlling clinical signs of hypoglycemia or the severity of polyuria and polydipsia has become unacceptable to the client. In the later situation, glucocorticoids should be continued but at a lower dose. The initial dosage of diazoxide is 5 mg/kg by mouth every 12 hours.

The dosage may gradually be increased as needed to control signs of hypoglycemia but should not exceed 60 mg/kg/day. Thiazide diuretics may potentiate the effects of diazoxide. The two drugs can be administered together to enhance hyperglycemic effects if diazoxide alone is not effective. The dosage of hydrochlorothiazide is 1 to 2 mg/kg by mouth every 12 hours.

The goal of diazoxide therapy is to establish a dosage at which hypoglycemia and its clinical signs are reduced or absent. In addition, the dosage should be low enough to avoid hyperglycemia (blood glucose concentrations > 180 mg/dL; 10 mmol/L) and its associated clinical signs. Reports of diazoxide use have appeared in the veterinary literature only sporadically (Leifer et al, 1986; Feldman and Nelson, 1987). Thirteen of 17 dogs with an insulin-secreting tumor in our series had a good clinical response, lasting 6 weeks to 20 months. In another report, nine of 14 dogs had a good response to diazoxide therapy (Leifer et al, 1986).

The most common adverse reactions to diazoxide administration are anorexia and vomiting. Administering diazoxide with a meal or decreasing the dosage, at least temporarily, is usually effective in controlling adverse gastrointestinal signs. Other potential complications include diarrhea, tachycardia, bone marrow suppression, aplastic anemia, thrombocytopenia, pancreatitis, diabetes mellitus, cataracts, and sodium and fluid retention (Feldman and Nelson, 1987). Diazoxide is metabolized in the liver, and the metabolites are excreted via the kidneys and biliary system. Adverse reactions or complications may develop more rapidly or at a lower dosage of diazoxide in a dog with concurrent hepatic dysfunction.

Somatostatin Therapy

Octreotide (Sandostatin) is an analog of somatostatin that inhibits the synthesis and secretion of insulin by normal and neoplastic beta cells. IV administration of octreotide can rapidly decrease the serum insulin concentration, causing a corresponding increase in the serum glucose concentration in dogs with insulin-secreting neoplasia (Robben et al, 1997; Fig. 9-14). The inhibitory actions of octreotide on insulin secretion can be maintained for several hours with subcutaneous administration (Fig. 9-15). The responsiveness of insulin-secreting tumors to the suppressive effects of octreotide varies and depends on the presence of membrane receptors on the tumor cells that bind somatostatin (Lamberts et al, 1990; Simpson et al, 1995). To date, five subtypes of somatostatin

receptors have been identified in humans (Patel, 1999). These subtypes show a tissue-specific distribution and differences in affinity for somatostatin and its analogs (Bruns et al, 1994). In humans, some insulin-secreting tumors have receptor subtypes that do not or only minimally bind octreotide, resulting in minimal to no effect by the analog on serum insulin and glucose concentrations (Lamberts et al, 1991; 1996). Autoradiography performed in dogs with insulin-secreting neoplasia suggests the presence of only one somatostatin receptor (sst2 receptors) in canine insulin-secreting tumors (Robben et al, 1997). The somatostatin receptor identified in canine insulin-secreting tumors contains high-affinity binding sites for octreotide and the radiopharmaceutical pentetreotide (see Scintigraphy). In that study, baseline plasma insulin concentrations, although varying widely, decreased significantly in all 10 dogs after octreotide administration. Unfortunately, octreotide is extremely expensive, must be administered by injection, has a relatively short (< 6 hours) suppressive effect on serum insulin concentrations in some dogs, clinical response to octreotide treatment is unpredictable, and some dogs that initially respond become refractory to octreotide treatment (Lothrop, 1989). Nevertheless, octreotide (10 to 40 µg SC twice or three times per day) is well tolerated and can be used for the management of both acute and chronic hypoglycemia in some dogs with insulin-secreting neoplasia. Adverse reactions have not been reported at these dosages.

Streptozotocin. Streptozotocin is a naturally occurring nitro-sourea that is similar in structure to glucose and is taken up by the GLUT-2 transmembrane carrier protein but not by other glucose transporters (Schnedl et al, 1994). Because pancreatic beta cells have high concentrations of GLUT-2 transporters, streptozotocin selectively destroys pancreatic beta cells by depressing the pyridine nucleotides nicotinamide adenine dinucleotide (NAD) and reduced nicotinamide adenine dinucleotide (NADH). Two dogs with confirmed hyperinsulinism were treated with streptozotocin by Meyer in the 1970s. The first dog developed nephrotoxicosis and was euthanized 3 weeks after a single treatment with streptozotocin at a dosage of 1000 mg/kg body weight given intravenously over a 1-minute period. The second dog developed temporary remission of hypoglycemia that lasted approximately 50 days after two treatments with streptozotocin at a dosage of 500 mg/m² given intravenously over a 30-second period. The treatments were given 1 week apart, and mannitol was infused for 20 minutes before and after each streptozotocin treatment. The

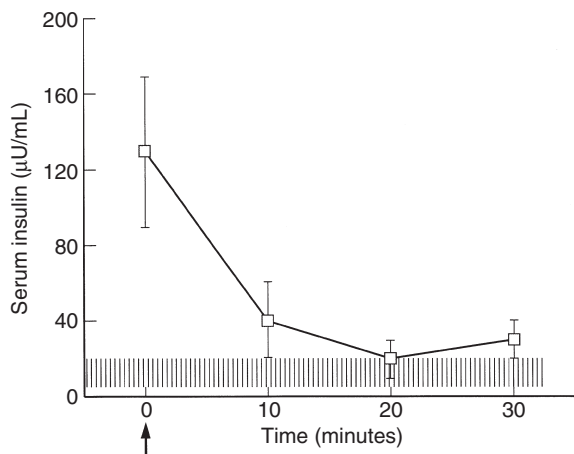


FIGURE 9-14 Mean (\pm SD) serum insulin concentration prior to and after intravenous (IV) administration of 100 µg of octreotide in six dogs with an insulin-secreting islet cell tumor. Arrow, Octreotide administration; hatched area, normal range for fasting serum insulin concentration.

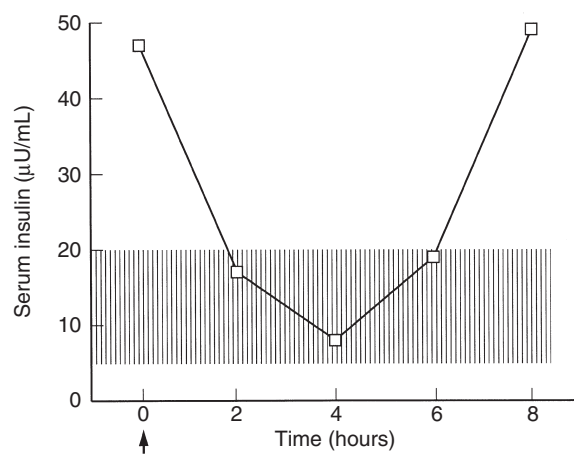


FIGURE 9-15 Serum insulin concentration prior to and after subcutaneous (SC) administration of 20 µg of octreotide to a dog with an insulin-secreting islet cell tumor. Arrow, Octreotide administration; hatched area, normal range for fasting serum insulin concentration.

dog developed a nephropathy and hepatopathy after a third treatment administered at day 97 and was euthanized shortly thereafter. As a result of these clinical reports, streptozotocin was not considered a viable treatment for insulin-secreting tumors in dogs.

In 2002, Moore and colleagues described a fluid diuresis protocol that allowed streptozotocin to be administered to dogs with insulin-secreting tumors with a minimum of adverse reactions. Fluid diuresis has been reported to ameliorate the renal toxicity of streptozotocin in humans, presumably as a result of less contact time between the drug and the renal tubular epithelium (Tobin et al, 1987; Kintzel, 2001). In Moore's study, diuresis with 0.9% sodium chloride at a rate of 18.3 mL/kg/hr administered through a peripherally located over-the-needle catheter was performed for 7 hours. Streptozotocin (Zanosar) was administered over a 2-hour period beginning 3 hours after initiation of the saline diuresis. The dose of streptozotocin (500 mg/m²) was diluted in an appropriate volume of 0.9% saline to maintain the same rate of fluid administration for 2 hours. Saline diuresis was continued at the same fluid rate for an additional 2 hours after completion of the streptozotocin administration. Butorphanol (0.4 mg/kg IV) was given immediately after streptozotocin administration as an antiemetic. Streptozotocin treatments were repeated at 3-week intervals until there was evidence of tumor progression (i.e., increase in tumor size by greater than 50%), recurrence of hypoglycemia, or streptozotocin-induced toxicity that required supportive treatment.

Fifty-eight treatments were administered to 17 dogs with an insulin-secreting tumor at variable times after surgery (Moore et al, 2002). Sixteen of 17 dogs had metastatic disease. One dog developed azotemia, several dogs developed increases in serum alanine aminotransferase activity that appeared to resolve with cessation of treatment, and vomiting occurred in 18 (31%) of 58 streptozotocin treatments and was occasionally severe. Two dogs developed diabetes mellitus after receiving five treatments; two of three dogs had rapid resolution of paraneoplastic peripheral neuropathy; and two dogs had a measurable reduction in tumor size. Although the median survival time was longer in dogs treated with streptozotocin than in 15 control dogs with a similar stage of disease (163 versus 90 days, respectively), this difference was not statistically significant. The range for survival time was also similar between the two groups of dogs (streptozotocin-treated dogs, 16 to 309 days; control dogs, 0 to 426 days).

Because myelosuppression was not observed in the Moore study, Northrup, et al., (2013) investigated increasing dose intensity by decreasing the interval between streptozotocin dosing from 3 to 2 week intervals. Nineteen dogs with residual, local, metastatic, or recurrent insulinoma were treated with the streptozotocin and saline diuresis protocol described by Moore, et al., (2002) but administered biweekly rather than once every 3 weeks. Treatment was initiated after surgery for insulinoma or at the time of recurrence. The planned treatment protocol was five treatments per dog; however, 13 dogs received fewer than five treatments (median, 3; range, 1 to 4) primarily because of development of adverse events. Adverse events occurred in all dogs and included nausea, anorexia, acute emesis or regurgitation, diarrhea, increased liver enzyme activity, renal tubular injury, and hypoglycemic collapse or seizure during treatment. Mild to moderate gastrointestinal toxicity was the most common adverse event. Myelosuppression was not identified. Eight dogs developed diabetes mellitus and six of these dogs subsequently died or were euthanized. Median survival time for the 19 dogs was 308 days (range, 20 to 1404 days; Fig. 9-16). Median progression-free survival time, defined as the number of days from the first streptozotocin treatment until recurrence

of hypoglycemia, detection of local recurrence or metastasis, or death because of any cause, was 196 days (range, 20 to 840 days). Response rate to streptozotocin could not be determined from the results of this study because there was no control group of dogs with comparable metastatic or nonresectable insulinoma that were not treated, and survival times in the streptozotocin-treated dogs were confounded by concurrent symptomatic therapy, use of other cytotoxic therapies, and owner decision to euthanize. Bell, et al., (2005) reported on a Springer Spaniel treated with glucocorticoids and one treatment of streptozotocin for metastatic insulinoma that subsequently developed diabetes mellitus. The dog was euthanized 118 days after streptozotocin treatment because of cervical pain caused by metastasis of the tumor.

In our experience, the effectiveness of streptozotocin in improving hypoglycemia, controlling clinical signs, and prolonging survival time has been unpredictable and adverse events to streptozotocin (severe vomiting, acute pancreatitis, potentially severe kidney injury) are common and can be life-threatening. A thorough discussion of potential complications with streptozotocin treatment should always be undertaken with the owner prior to initiating treatment.

Phenytoin. Phenytoin is an anticonvulsant that inhibits the release of insulin by beta cells and may also directly impair the effects of insulin on peripheral tissues (Haemers and Rottiers, 1981). Unfortunately, phenytoin is not usually successful in controlling clinical signs of hypoglycemia. Only 30% of human patients with hyperinsulinism showed any beneficial effects after phenytoin administration (Haemers and Rottiers, 1981). Concurrent diazoxide administration is not recommended, because it results in a decrease in blood concentrations of phenytoin. Phenytoin has not been critically evaluated in dogs with beta-cell neoplasia.

Propranolol. Propranolol is a nonselective beta-adrenergic blocking drug that has no intrinsic sympathomimetic activity. Its potential usefulness in patients with beta-cell neoplasia probably involves its ability to block insulin secretion by beta cells. Insulin secretion is stimulated by the beta-adrenergic nervous system. However, propranolol may also induce hypoglycemia by impairing hepatic gluconeogenesis and glycogenolysis, normally induced by endogenous catecholamines. Propranolol has not been critically evaluated in dogs with beta cell neoplasia.

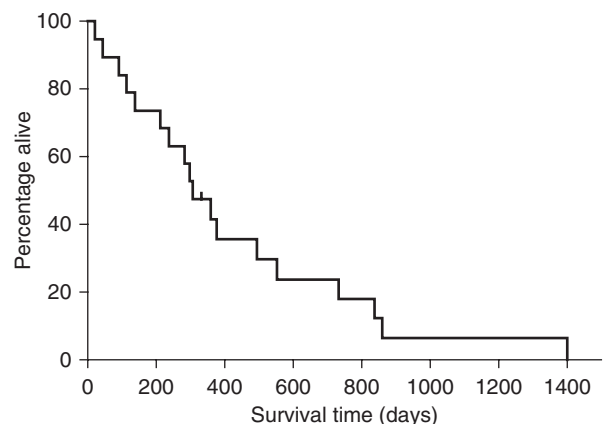


FIGURE 9-16 Kaplan-Meier curve depicting overall survival of 19 dogs with insulinoma treated with streptozotocin at 2-week intervals. The median survival time was 308 days (range, 20 to 1404 days). (From Northrup NC, et al.: Prospective evaluation of biweekly streptozotocin in 19 dogs with insulinoma, *J Vet Intern Med* 27:483, 2013.)



PROGNOSIS

Owing to the extremely high likelihood of malignancy in any dog with an insulin-secreting tumor (greater than 95%), the long-term prognosis is guarded to poor at best because beta-cell tumors almost always metastasize. The disease-free interval and survival time are difficult to predict. Survival time depends partly on the owner's willingness to treat the disease. Predictors of disease free interval and survival time in dogs with an insulin-secreting beta-cell tumor include tumor size, TNM (tumor, node, and metastasis) stage, stromal fibrosis within the tumor, and the Ki67 index (Caywood et al, 1988; Buishand et al, 2010). Ki67 is a proliferation marker expressed during the active phases of the cell cycle and absent in resting cells (Scholzen and Gerdes, 2000). The Ki67 index has been correlated with clinical outcome in humans with insulinoma (La Rosa et al, 2009).

Tobin and colleagues (1999) reported median survival time after diagnosis of 74 days (range, 8 to 508 days) and 381 days (range, 20 to 1758) in dogs treated medically versus dogs that initially underwent surgery followed by medical treatment, respectively. Polton and colleagues (2007) reported median survival time after diagnosis of 196 days (95% confidence interval [CI] 0 to 549 days) and 785 days (95% CI: 190 to 1380 days) in dogs treated medically versus dogs that initially underwent surgery followed by medical treatment, respectively. The shorter survival time for dogs treated medically in the Tobin study was partly due to a more severe stage of the disease at the time of diagnosis and the owners' feelings of hopelessness, which translated into early acceptance of euthanasia when clinical signs recurred. Polton, et al., (2007) reported a median disease free interval of 496 days (95% CI: 302 to 690 days) in 19 dogs that underwent partial pancreatectomy. The median disease free interval in 31 dogs that underwent partial pancreatectomy at Utrecht University was 244 days (range, 0 to 1116 days) and survival time was 258 days (range, 1 to 1146) (Tryfonidou et al, 1998).

The extent to which surgery can alter the prognosis depends on the clinical stage of the disease, most notably the extent of metastatic lesions. In one multi-university study, dogs with tumors confined to the pancreas (stage I) were normoglycemic for a median of 14 months after surgery, whereas dogs with metastasis to regional lymph nodes (stage II) or distant metastasis (stage III) were normoglycemic for a median of approximately 1 month (Caywood et al, 1988). Dogs with stage I or stage II disease had a median survival time of approximately 18 months, whereas those with stage III disease had a median survival time of less than 6 months. Approximately 50% of dogs with metastases to the liver were dead by 6 months, and all were dead by 18 months from the time of diagnosis.

In our experience, approximately 10% to 15% of dogs undergoing surgery for an insulin-secreting tumor die or are euthanized at the time of or within 1 month of surgery because of severe metastatic disease, uncontrollable postoperative hypoglycemia, or complications related to pancreatitis. An additional 20% to 25% of dogs die or are euthanized within 6 months of surgery because of severe metastatic disease and recurrence of clinical hypoglycemia. The remaining 60% to 70% live beyond 6 months postoperatively, many beyond 1 year after surgery, before uncontrollable hypoglycemia develops, resulting in death or necessitating euthanasia. Additional surgery to debulk metastatic lesions may improve the animal's responsiveness to medical therapy and prolong the survival time in some dogs that become nonresponsive to medical treatment after the initial surgery. Some dogs with metastatic disease do remarkably well (i.e., survive longer than 2 years) after aggressive surgical debulking of the tumor and its metastases.



INSULIN-SECRETING BETA-CELL TUMORS IN CATS

Insulin-secreting beta-cell tumors are rare in cats with only a few single cat case reports in the literature (McMillan, 1985; O'Brien et al, 1990; Hawks et al, 1992; Kraje, 2003; Greene and Bright, 2008) and one additional report in which the beta-cell tumor was an incidental finding at necropsy in a cat with ductal pancreatic adenocarcinoma (Carpenter et al, 1987). We have seen only two cats with beta-cell neoplasia during the past three decades, in contrast to more than 150 dogs with the disease during the same time interval.

The clinical characteristics of insulin-secreting beta-cell tumors in cats appear to be similar to those in dogs. To date, the disorder has affected aged cats, 12 to 17 years old. Interestingly, three cats have been Siamese. Immunohistochemical analysis of the beta-cell tumor in a few of these cats has revealed multihormonal productivity, with insulin and chromogranin A being the most common peptides demonstrated in the neoplastic cells (Kraje, 2003; Jackson et al, 2009). Clinical signs result from the effects of hyperinsulinism and included seizures, weakness, ataxia, lethargy, disorientation, and muscle twitching. Hypoglycemia (blood glucose concentration < 60 mg/dL; 3.4 mmol/L) was documented in each cat, and an inappropriately increased blood insulin concentration was documented in four cats in which insulin was measured. Abdominal ultrasound failed to identify a 1.5 to 2.0 cm pancreatic mass in one cat and a 0.4 cm pancreatic mass in another cat in which ultrasound was performed prior to surgery. A pancreatic mass was identified in five cats that underwent surgery, and hypoglycemia and clinical signs resolved in four of five cats after surgical excision of the mass. Four cats died or were euthanized 4 weeks, 5 weeks, 18 months, and 2 years after surgery, and three of these four cats were hypoglycemic at the time of death. Necropsy in one of these cats revealed metastasis to the liver and pancreatic lymph nodes. One cat was alive with no clinical signs suggestive of recurrence of the insulinoma 32 months after surgical removal of a solitary 0.4 cm pancreatic carcinoma (Greene and Bright, 2008).

Until more experience is gained with beta-cell neoplasia in cats, it seems prudent to approach this disorder in a manner similar to that used for dogs. Beta-cell neoplasia should be included in the list of differential diagnoses for persistent hypoglycemia in the older cat (see Box 9-4). The index of suspicion for beta-cell neoplasia should be heightened after a thorough review of the history, physical examination, and results of clinicopathologic tests and diagnostic imaging. However, as with the dog, failure to identify a pancreatic mass with abdominal ultrasound does not rule out a beta cell tumor. The diagnosis should be confirmed by documentation of an inappropriate serum insulin concentration despite the presence of hypoglycemia (see Confirming the Diagnosis of an Insulin-Secreting Beta-Cell Tumor: Serum Insulin Determination). Many commercially available radioimmunoassays for insulin work well in the dog but do not work in the cat (Lutz and Rand, 1993). It is imperative that the radioimmunoassay used to measure feline insulin is validated for cats and that species specific reference ranges are available.

Surgical exploration should be the initial treatment of choice for beta-cell neoplasia in the cat. However, the age of the cat, identification of metastatic disease using ultrasonography, or the existence of concurrent disease that increases the anesthetic risk may warrant a more conservative medical approach in some cats. Frequent feedings and prednisolone therapy have been effective in controlling clinical signs of hyperinsulinism and should be the mainstay of medical therapy for chronic hypoglycemia. The use of diazoxide has not been reported in the cat and is not recommended until its safety and dosing schedule have been investigated in cats. Similarly, the efficacy of octreotide for the treatment of feline beta-cell neoplasia remains to be reported.

REFERENCES

- Bagley RS, et al.: Hypoglycemia associated with intraabdominal leiomyoma and leiomyosarcoma in six dogs, *J Am Vet Med Assoc* 208:69, 1996.
- Barreca A, et al.: In vitro paracrine regulation of human keratinocyte growth by fibroblast-derived insulin-like growth factors, *J Cell Physiol* 151:262, 1992.
- Beaudry D, et al.: Hypoglycemia in four dogs with smooth muscle tumors, *J Vet Intern Med* 9:415, 1995.
- Bell R, et al.: Treatment of insulinoma in a springer spaniel with streptozotocin, *J Sm Anim Pract* 46:247, 2005.
- Bellah JR, Ginn PE: Gastric leiomyosarcoma associated with hypoglycemia in a dog, *J Am Anim Hosp Assoc* 32:283, 1996.
- Bergman PJ, et al.: Canine clinical peripheral neuropathy associated with pancreatic islet cell carcinoma, *Prog Vet Neurol* 5:57, 1994.
- Boari A, et al.: Hypoglycemia in a dog with a leiomyoma of the gastric wall producing an insulin-like growth factor II-like peptide, *Eur J Endocrinol* 132:744, 1995.
- Boyle PJ, Cryer PE: Growth hormone, cortisol, or both are involved in defense against but are not critical to recovery from prolonged hypoglycemia in humans, *Am J Physiol* 260:E395, 1991.
- Braund KG, et al.: Insulinoma and subclinical peripheral neuropathy in two dogs, *J Vet Intern Med* 1:86, 1987.
- Breitschwerdt EB, et al.: Hypoglycemia in four dogs with sepsis, *J Am Vet Med Assoc* 178:1072, 1981.
- Brix A, et al.: Glycogen storage disease type Ia in two littermate Maltese puppies, *Vet Pathol* 32:460, 1995.
- Bruns C, et al.: Molecular pharmacology of somatostatin receptor subtypes, *Ann N Y Acad Sci* 733:138, 1994.
- Buetow PC, et al.: Islet cell tumors of the pancreas: clinical, radiological, and pathologic correlation in diagnosis and localization, *Radiographics* 17:453, 1997.
- Buishand FO, et al.: Evaluation of clinicopathological criteria and the Ki67 index as prognostic indicators of canine insulinoma, *Vet J* 185:62, 2010.
- Buishand FO, et al.: Expression of insulin-like growth factor-1 by canine insulinomas and their metastases, *Vet J* 191:334, 2012.
- Buse JB, et al.: Type 2 diabetes mellitus. In Melmed S, Polonsky K, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Elsevier, p 1371.
- Caceres AV, et al.: Helical computed tomographic angiography of the normal canine pancreas, *Vet Radiol Ultrasound* 47:270, 2006.
- Carpenter JL, et al.: Tumors and tumorlike lesions. In Holsworth J, editor: *Diseases of the cat: medicine and surgery*, Philadelphia, 1987, WB Saunders, p 406.
- Caywood DD, et al.: Pancreatic insulin-secreting neoplasms: clinical, diagnostic, and prognostic features in 73 dogs, *J Am Anim Hosp Assoc* 24:577, 1988.
- Chastain CB: Endocrine and metabolic systems. In Hoskins JD, editor: *Veterinary pediatrics*, Philadelphia, 1990, WB Saunders, p 249.
- Chatziioannou A, et al.: Imaging and localization of pancreatic insulinomas, *Clin Imaging* 25:275, 2001.
- Chew DJ, et al.: Hyperglycemia and hypoglycemia. In Klenner WR, editor: *Quick reference to veterinary medicine*, Philadelphia, 1982, JB Lippincott, p 432.
- Cohen M, et al.: Gastrointestinal leiomyosarcoma in 14 dogs, *J Vet Intern Med* 17:107, 2003.
- Cohen TA, et al.: Evaluation of six portable blood glucose meters for measuring blood glucose concentration in dogs, *J Am Vet Med Assoc* 235:276, 2009.
- Cohn LA, et al.: Assessment of five portable blood glucose meters, a point-of-care analyzer, and color test strips for measuring blood glucose concentration in dogs, *J Am Vet Med Assoc* 216:198, 2000.
- Commens PJ, et al.: Interleukin-1 is a potent modulator of insulin secretion from isolated rat islets of Langerhans, *Diabetes* 36:963, 1987.
- Cryer PE: Catecholamines, pheochromocytoma and diabetes, *Diabetes Rev* 1:309, 1993.
- Cryer PE: Hypoglycemia. In Melmed S, Polonsky K, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Elsevier, p 1552.
- Cryer PE, Gerich JE: Glucose counterregulation, hypoglycemia, and intensive insulin therapy in diabetes mellitus, *N Engl J Med* 313:232, 1985.
- Cryer PE, Polonsky KS, et al.: Glucose homeostasis and hypoglycemia. In Wilson JD, editor: *Williams textbook of endocrinology*, ed 9, Philadelphia, 1998, WB Saunders, p 939.
- Das H, Hochberg FH: Metastatic neoplasms and paraneoplastic syndromes. In Goetz CG, Pappert EJ, editors: *Textbook of clinical neurology*, Philadelphia, 1999, WB Saunders, p 957.
- D'Ercole AJ, et al.: Tissue concentrations of somatomedin C: further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action, *Proc Natl Acad Sci USA* 81:935, 1984.
- de Bruijne JJ, et al.: Fat mobilization and plasma hormone levels in fasted dogs, *Metabolism* 30:190, 1981.
- de Groot JW, et al.: Non-islet cell tumor-induced hypoglycaemia: a review of the literature including two new cases, *Endocr Relat Cancer* 14:979, 2007.
- del Rey A, Besedovsky H: Interleukin 1 affects glucose homeostasis, *Am J Physiol* 253:R794, 1987.
- Edwards DF, et al.: Hypoglycemia and chronic renal failure in a cat, *J Am Vet Med Assoc* 190:435, 1987.
- Feldman EC, Nelson RW: *Canine and feline endocrinology and reproduction*, Philadelphia, 1987, WB Saunders.
- Fenner WR: Diseases of the brain. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine*, ed 4, Philadelphia, 1995, WB Saunders, p 578.
- Fingerth JM, Smeak DD: Intravenous methylene blue infusion for intraoperative identification of pancreatic islet cell tumors in dogs. II. Clinical trials and results in four dogs, *J Am Anim Hosp Assoc* 24:175, 1988.
- Fingerth JM, et al.: Intravenous methylene blue infusion for intraoperative identification of parathyroid gland and pancreatic islet cell tumors in dogs. I. Experimental determination of dose-related staining efficacy and toxicity, *J Am Anim Hosp Assoc* 24:165, 1988.
- Finotello R, et al.: Pancreatic islet cell tumor secreting insulin-like growth factor type-II in a dog, *J Vet Intern Med* 23:1289, 2009.
- Fischer JR, et al.: Glucagon constant-rate infusion: a novel strategy for the management of hyperinsulinemic-hypoglycemic crisis in the dog, *J Am Anim Hosp Assoc* 36:27, 2000.
- Fischer KF, et al.: Hypoglycemia in hospitalized patients: causes and outcomes, *N Engl J Med* 315:1245, 1986.
- Fyfe JC, et al.: Glycogen storage disease type IV: inherited deficiency of branching enzyme activity in cats, *Pediatr Res* 32:719, 1992.
- Garden OA, et al.: Somatostatin receptor imaging in vivo by planar scintigraphy facilitates the diagnosis of canine insulinomas, *J Vet Intern Med* 19:168, 2005.
- Gerich J, et al.: Hypoglycemia unawareness, *Endocr Rev* 12:356, 1991.
- Gerich JE, et al.: Renal gluconeogenesis: its importance in human glucose homeostasis, *Diabetes Care* 24:382, 2001.
- Giger U, et al.: Metabolic myopathy in canine muscle-type phosphofructokinase deficiency, *Muscle Nerve* 11:1260, 1988.
- Greene SN, Bright RM: Insulinoma in a cat, *J Sm Anim Pract* 49:38, 2008.
- Gregory BL, et al.: Glycogen storage disease type IIIa in curly-coated retrievers, *J Vet Intern Med* 21:40, 2007.
- Gritzmann N, et al.: CT in the differentiation of pancreatic neoplasms-progress report, *Dig Dis* 22:6, 2004.
- Guedes AG, Rude EP: Effects of pre-operative administration of medetomidine on plasma insulin and glucose concentrations in healthy dogs and dogs with insulinoma, *Vet Anaesth Analg* 40:472, 2013.
- Haemers S, Rottiers R: Medical treatment of insulinoma, *Acta Clin Belg* 36:199, 1981.
- Hambrook LY, Kudnig ST: Tumor thrombus formation in two dogs with insulinoma, *J Am Vet Med Assoc* 241:1065, 2012.
- Hardy RM: Diseases of the liver and their treatment. In Ettinger SJ, editor: *Textbook of veterinary internal medicine*, ed 3, Philadelphia, 1989, WB Saunders, p 1479.
- Hargrove DM, et al.: Adrenergic blockade does not abolish elevated glucose turnover during bacterial infection, *Am J Physiol* 254:E16, 1988a.

- Hargrove DM, et al.: Adrenergic blockade prevents endotoxin-induced increases in glucose metabolism, *Am J Physiol* 255:E629, 1988b.
- Hawkins KL, et al.: Immunocytochemistry of normal pancreatic islets and spontaneous islet cell tumors in dogs, *Vet Pathol* 24:170, 1987.
- Hawks D, et al.: Insulin-secreting pancreatic (islet cell) carcinoma in a cat, *J Vet Intern Med* 6:193, 1992.
- Heckmann JG, et al.: Hypoglycemic sensorimotor polyneuropathy associated with insulinoma, *Muscle Nerve* 23:1891, 2000.
- Hooper AN, Roberts BK: Fanconi syndrome in four non-basenji dogs exposed to chicken jerky treats, *J Amer Anim Hosp Assoc* 47:178, 2011.
- Iseri T, et al.: Dynamic computed tomography of the pancreas in normal dogs and in a dog with pancreatic insulinoma, *Vet Radiol Ultrasound* 48:328, 2007.
- Jackson TC, et al.: Cellular and molecular characterization of a feline insulinoma, *J Vet Intern Med* 23:383, 2009.
- Jeffery ND, et al.: Letter to the editor, *Prog Vet Neurol* 5:135, 1994.
- Karam JH: Hypoglycemic disorders. In Greenspan FS, Gardner DG, editors: *Basic and clinical endocrinology*, ed 6, New York, 2001, Lange Medical Books/McGraw-Hill, p 699.
- Kintzel PE: Anticancer drug-induced kidney disorders, *Drug Safety* 24:19, 2001.
- Kishnani PS, et al.: Isolation and nucleotide sequence of canine glucose-6-phosphatase mRNA: identification of mutation in puppies with glycogen storage disease type Ia, *Biochem Mol Med* 61:168, 1997.
- Kishnani PS, et al.: Canine model and genomic structural organization of glycogen storage disease type Ia (GSD Ia), *Vet Pathol* 38:83, 2001.
- Kraje AC: Hypoglycemia and irreversible neurologic complications in a cat with insulinoma, *J Am Vet Med Assoc* 223:812, 2003.
- Kruth SA, et al.: Insulin-secreting islet cell tumors: establishing a diagnosis and the clinical course of 25 dogs, *J Am Vet Med Assoc* 181:54, 1982.
- Kudo M, Noguchi T: Immunoreactive myelin basic protein in tumor cells associated with carcinomatous neuropathy, *Am J Clin Pathol* 84:741, 1985.
- Kvols LK, et al.: Evaluation of a radio-labeled somatostatin analog (I-123 octreotide) in the detection and localization of carcinoid and islet cell tumors, *Radiology* 197:129, 1993.
- La Rosa S, et al.: Improved histologic and clinicopathologic criteria for prognostic evaluation of pancreatic endocrine tumors, *Human Path* 40:30, 2009.
- Lamb CR, et al.: Ultrasonography of pancreatic neoplasia in the dog: a retrospective review of 16 cases, *Vet Rec* 137:65, 1995.
- Lamberts S, et al.: Parallel in vivo and in vitro detection of functional somatostatin receptors in human endocrine pancreatic tumors: consequences with regard to diagnosis, localization and therapy, *J Clin Endocrinol Metab* 71:566, 1990.
- Lamberts SJW, et al.: The role of somatostatin and its analogs in the diagnosis and treatment of tumors, *Endocrinol Rev* 12:450, 1991.
- Lamberts SJW, et al.: Octreotide and related somatostatin analogs in the diagnosis and treatment of pituitary disease and somatostatin receptor scintigraphy, *Neuroendocrinology* 14:27, 1993.
- Lamberts SWJ, et al.: Somatostatin analogs: future directions, *Metabolism* 45:104, 1996.
- Leifer CE, et al.: Insulin-secreting tumor: diagnosis and medical and surgical management in 55 dogs, *J Am Vet Med Assoc* 188:60, 1986.
- Lester NV, et al.: Scintigraphic diagnosis of insulinoma in a dog, *Vet Radiol Ultrasound* 40:174, 1999.
- Loftin EG, Herold LV: Therapy and outcome of suspected alpha lipoic acid toxicity in two dogs, *J Vet Emerg Crit Care* 19:501, 2009.
- Lothrop CD: Medical treatment of neuroendocrine tumors of the gastroenteropancreatic system with somatostatin. In Kirk RW, editor: *Current veterinary therapy X*, Philadelphia, 1989, WB Saunders, p 1020.
- Lutz TA, Rand JS: Comparison of five commercial radioimmunoassay kits for the measurement of feline insulin, *Res Vet Sci* 55:64, 1993.
- Madarame H, et al.: Retrospective study of canine insulinomas: eight cases (2005-2008), *J Vet Med Sci* 71:905, 2009.
- Mai W, Caceres AV: Dual-phase computed tomographic angiography in three dogs with pancreatic insulinoma, *Vet Radiol Ultrasound* 49:141, 2008.
- McMillan F: Functional pancreatic islet cell tumor in a cat, *J Am Anim Hosp Assoc* 21:741, 1985.
- Mehlhoff CJ, et al.: Insulin-producing islet cell neoplasms: surgical considerations and general management in 35 dogs, *J Am Anim Hosp Assoc* 21:607, 1985.
- Mellanby RJ, Herrtage ME: Insulinoma in a normoglycaemic dog with low serum fructosamine, *J Sm Anim Pract* 43:506, 2002.
- Meszáros K, et al.: Increased uptake and phosphorylation of 2-deoxyglucose by skeletal muscles in endotoxin-treated rats, *Am J Physiol* 253:E33, 1987.
- Meszáros K, et al.: In vivo glucose utilization by individual tissues during nonlethal hypermetabolic sepsis, *FASEB J* 2:3083, 1988.
- Meyer C, et al.: Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients, *Diabetes Care* 21:1960, 1998.
- Minkus G, et al.: Canine neuroendocrine tumors of the pancreas: a study using image analysis techniques for the discrimination of metastatic versus nonmetastatic tumors, *Vet Pathol* 34:138, 1997.
- Mokan M, et al.: Hypoglycemia unawareness in IDDM, *Diabetes Care* 17:1397, 1994.
- Moore AS, et al.: Streptozotocin for treatment of pancreatic islet cell tumors in dogs: 17 cases (1989-1999), *J Am Vet Med Assoc* 221:811, 2002.
- Murphy LA, Coleman AE: Xylitol toxicosis in dogs, *Vet Clin N Am Small Anim* 42:307, 2012.
- Naylor JM, Kronfeld DS: In vivo studies of hypoglycemia and lactic acidosis in endotoxic shock, *Am J Physiol* 248:E309, 1985.
- Niessen SJM: Glucagon: are we missing a (life-saving) trick? *J Vet Emerg Crit Care* 22:523, 2012.
- Northrup NC, et al.: Prospective evaluation of biweekly streptozotocin in 19 dogs with insulinoma, *J Vet Intern Med* 27:483, 2013.
- Öberg J, et al.: Validation of a species-optimized enzyme-linked immunosorbent assay for determination of serum concentrations of insulin in dogs, *Vet Clin Path* 40:66, 2011.
- O'Brien TD, et al.: Canine pancreatic endocrine tumors: Immunohistochemical analysis of hormone content and amyloid, *Vet Pathol* 24:308, 1987.
- O'Brien TD, et al.: Pancreatic endocrine tumor in a cat: clinical, pathological, and immunohistochemical evaluation, *J Am Anim Hosp Assoc* 26:453, 1990.
- Patel YC: Somatostatin and its receptor family, *Front Neuroendocrinol* 20:157, 1999.
- Pickens EH, et al.: Unique radiographic appearance of bone marrow metastasis of an insulin-secreting beta-cell carcinoma in a dog, *J Vet Intern Med* 19:350, 2005.
- Polton GA, et al.: Improved survival in a retrospective cohort of 28 dogs with insulinoma, *J Sm Anim Pract* 48:151, 2007.
- Reubi J, et al.: Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands, *Eur J Nucl Med* 28:836, 2001.
- Robben JH, et al.: In vitro and in vivo detection of functional somatostatin receptors in canine insulinomas, *J Nucl Med* 38:1036, 1997.
- Robben JH, et al.: Comparison of ultrasonography, computed tomography, and single-photon emission computed tomography for the detection and localization of canine insulinoma, *J Vet Intern Med* 19:15, 2005.
- Rossi G, et al.: Paraneoplastic hypoglycemia in a diabetic dog with an insulin growth factor-2-producing mammary carcinoma, *Vet Clin Path* 39:480, 2010.
- Rothman DL, et al.: Quantitation of hepatic glycogenolysis and gluconeogenesis in fasting humans with ¹³C NMR, *Science* 254:573, 1991.

- Schnedl WJ, et al.: STZ transport and cytotoxicity; specific enhancement of GLUT2-expressing cells, *Diabetes* 43:1326, 1994.
- Scholzen T, Gerdes J: The Ki-67 protein: from the known and the unknown, *J Cell Physiol* 182:311, 2000.
- Schrauwen E, et al.: Peripheral polyneuropathy associated with insulinoma in the dog: clinical, pathological, and electrodiagnostic features, *Prog Vet Neurol* 7:16, 1996.
- Service FJ: Hypoglycemic disorders, *N Engl J Med* 332:1144, 1995.
- Shahar R, et al.: Peripheral neuropathy in a dog with functional islet B-cell tumor and widespread metastasis, *J Am Vet Med Assoc* 187:175, 1985.
- Sherwin RS, Felig P: Hypoglycemia. In Felig P, et al.: *Endocrinology and metabolism*, New York, 1981, McGraw-Hill, p 869.
- Simpson KW, et al.: Evaluation of the long-acting somatostatin analogue octreotide in the management of insulinoma in three dogs, *J Small Anim Pract* 36:161, 1995.
- Slye M, Wells HG: Tumor of islet tissue with hyperinsulinism in a dog, *Arch Pathol* 19:537, 1935.
- Smeak DD, et al.: Intravenous methylene blue as a specific stain for primary and metastatic insulinoma in a dog, *J Am Anim Hosp Assoc* 24:478, 1988.
- Smith BF, et al.: Molecular basis of canine muscle type phosphofructokinase deficiency, *J Biol Chem* 271:20070, 1996.
- Stumvoll M, et al.: Uptake and release of glucose by the human kidney: postabsorptive rates and responses to epinephrine, *J Clin Invest* 96:2528, 1995.
- Thompson MF, et al.: Acquired proximal renal tubulopathy in dogs exposed to a common dried chicken treat: retrospective study of 108 cases (2007-2009), *Aust Vet J* 91:368, 2013.
- Thorens B, Mueckler M: Glucose transporters in the 21st century, *Am J Physiol Endocrinol Metab* 298:E141, 2010.
- Tobin MV, et al.: Forced diuresis to reduce nephrotoxicity of streptozocin in the treatment of advanced metastatic insulinoma, *Br Med J* 294:1128, 1987.
- Tobin RL, et al.: Outcome of surgical versus medical treatment of dogs with beta-cell neoplasia: 39 cases (1990-1997), *J Am Vet Med Assoc* 215:226, 1999.
- Tryfonidou MA, et al.: A retrospective evaluation of 51 dogs with insulinoma, *Vet Quart* 20:114, 1998.
- Van Ham L, et al.: Treatment of a dog with an insulinoma-related peripheral polyneuropathy with corticosteroids, *Vet Rec* 141:98, 1997.
- Van Hoe L, et al.: Helical CT for the preoperative localization of islet cell tumors of the pancreas: value of arterial and parenchymal phase images, *Am J Roentgenol* 165:1437, 1995.
- Walvoort HC, et al.: Comparative pathology of the canine model of glycogen storage disease type II (Pompe's disease), *J Inherit Metab Dis* 8:38, 1985.
- Wess G, Reusch C: Evaluation of five portable blood glucose meters for use in dogs, *J Am Vet Med Assoc* 216:203, 2000.
- Whipple AO, Grantz VK: Adenoma of islet cells with hyperinsulinism: a review, *Ann Surg* 101:1299, 1935.
- Zeugswetter FK, et al.: Metabolic and hormonal responses to subcutaneous glucagon in healthy beagles, *J Vet Emerg Crit Care* 22:558, 2012.
- Zini E, et al.: Paraneoplastic hypoglycemia due to an insulin-like growth factor type-II secreting hepatocellular carcinoma, *J Vet Intern Med* 21:193, 2007.
- Zini E, et al.: Evaluation of a new portable glucose meter designed for use in cats, *Schweiz Arch Tierheilkd* 151:448, 2009.