SECTION 3 | THE ENDOCRINE PANCREAS

CHAPTER 6

Canine Diabetes Mellitus

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CHAPTER CONTENTS

The endocrine pancreas is composed of the islets of Langerhans, which are dispersed as "small islands" in a "sea" of exocrine-secreting acinar cells. Four distinct cell types have been identified within these islets on the basis of staining properties and morphology—alpha cells, which secrete glucagon; beta cells, which secrete insulin; delta cells, which secrete somatostatin; and pancreatic polypeptide (PP) cells, which secrete pancreatic polypeptide. Dysfunction involving any of these cell lines ultimately results in either an excess or a deficiency of the respective hormone in the circulation. In the dog and cat, the most common disorder of the endocrine pancreas is diabetes mellitus, which results from an absolute or relative insulin deficiency due to deficient insulin secretion by the beta cells, often in conjunction with concurrent insulin resistance. The incidence of diabetes mellitus in dogs varies between countries. The largest study, to date, involved 180,000 insured dogs in Sweden and researchers estimated the cumulative

proportion of dogs that would develop diabetes mellitus before 12 years of age at 1.2% (Fall et al, 2007). Davison, et al., (2005) reported from a UK insurance cohort a diabetes mellitus prevalence of 0.32%; Guptill, et al., (2003) reported a hospital prevalence of 0.64% in the United States; and Fracassi, et al., (2004) reported an Italian hospital prevalence of 1.33%.

CLASSIFICATION AND ETIOLOGY

Type 1 Diabetes Mellitus

The most common clinically recognized form of diabetes mellitus in the dog resembles type 1 diabetes mellitus in humans. In our hospital, virtually all dogs are insulin dependent at the time diabetes mellitus is diagnosed. Type 1 diabetes mellitus is characterized by permanent hypoinsulinemia, essentially no increase in endogenous serum insulin concentration following administration of an insulin secretagogue (e.g., glucose, glucagon), and an absolute necessity for exogenous insulin to maintain control of glycemia, avoid ketoacidosis, and survive. The etiology of type 1 diabetes has been poorly characterized in dogs but is undoubtedly multifactorial (Table 6-1). Genetic predispositions have been suggested by familial associations, pedigree analysis of Keeshonds, and genomic studies aimed at identification of susceptibility and protective major histocompatibility complex haplotypes in canine diabetes (Hess et al, 2000a; Guptill et al, 2003; Fracassi et al, 2004; Kennedy et al, 2006; Fall et al, 2007; Table 6-2). A number of genes linked with susceptibility to diabetes mellitus in humans are associated with an increased risk of diabetes mellitus in dogs (Catchpole et al, 2013). Diabetes mellitus in dogs has been associated with major histocompatibility complex class II genes, dog leucocyte antigen (DLA), with similar haplotypes and genotypes being identified in the most susceptible breeds. A region containing a variable number of tandem repeats and several polymorphisms have been identified in the canine insulin gene with some alleles associated with susceptibility or resistance to diabetes in a breed-specific manner (Catchpole et al, 2013).

Common histologic abnormalities in dogs include a reduction in the number and size of pancreatic islets, a decrease in the number of beta cells within islets, and beta cell vacuolation and degeneration. An extreme form of the disease may occur in juvenile dogs, represented by an absolute deficiency of beta cells and pancreatic islet hypoplasia or aplasia. Less severe changes of pancreatic islets and beta cells may predispose the adult dog to diabetes mellitus after it has been exposed to environmental factors, such as insulin-antagonistic diseases and drugs, obesity, and pancreatitis. Environmental factors may induce beta cell degeneration secondary to chronic insulin resistance or may cause release of beta cell proteins, which induce immune-mediated destruction of the islets (Nerup, 1994).

Studies suggest an immune-mediated component in the development of diabetes in some dogs. Immune-mediated insulitis has been described and antibodies directed against islet cells, insulin, proinsulin, intracellular glutamic acid decarboxylase 65 (GAD65), and insulinoma antigen 2 (IA-2) have been identified in diabetic dogs (Hoenig and Dawe, 1992; Alejandro et al, 1988; Davison et al, 2003a; 2008a; 2011; these are autoantibodies that are also identified in humans with type 1 diabetes. The presence of circulating autoantibodies against insulin, proinsulin, GAD65, and IA-2 usually precede the development of hyperglycemia or clinical signs in humans with type 1 diabetes. A similar sequence of events may also occur in dogs, although the onset of type 1 diabetes mellitus occurs in young humans versus older dogs. Canine diabetes more closely resembles latent autoimmune diabetes of adult humans (Andersen et al, 2010). Seemingly, autoimmune mechanisms in conjunction with genetic and environmental factors, insulin-antagonistic diseases and drugs, obesity, and pancreatitis all play a potential role in the initiation and progression of diabetes in dogs. The end result is a loss of beta-cell function, hypoinsulinemia, impaired transport of circulating glucose into most cells, and accelerated hepatic gluconeogenesis and glycogenolysis. The subsequent development of hyperglycemia and glycosuria causes polyuria, polydipsia, polyphagia, and weight loss. Ketoacidosis develops as the production of ketone bodies increases to compensate for the underutilization of blood glucose. Loss of beta-cell function is irreversible in dogs with type 1 diabetes, and lifelong insulin therapy is mandatory to maintain glycemic control of the diabetic state.

Clinically, pancreatitis is often seen in dogs with diabetes mellitus and has been suggested as a cause of diabetes after destruction of the islets (Watson et al, 2010; Bostrom et al, 2013). However, the incidence of histologically identifiable pancreatitis in diabetic dogs is only 30% to 40%. Although destruction of beta cells secondary to pancreatitis is an obvious explanation for the development of hypoinsulinemic diabetes mellitus, other perhaps more complex factors are involved in the development of diabetes mellitus in dogs without obvious exocrine pancreatic lesions.

TABLE 6-1 **POTENTIAL FACTORS INVOLVED IN THE ETIOPATHOGENESIS OF DIABETES MELLITUS IN DOGS AND CATS**

DOG	CAT
Genetics	Islet amyloidosis
Immune-mediated insulitis	Obesity
Pancreatitis	Pancreatitis
Obesity	Concurrent hormonal disease
Concurrent hormonal disease	Hyperadrenocorticism
Hyperadrenocorticism	Acromegaly
Diestrus-induced excess of growth hormone	Hyperthyroidism
Hypothyroidism	Drugs
Drugs	Progestagens
Glucocorticoids	Glucocorticoids
Progestagens	Infection
Infection	Concurrent illness
Concurrent illness	Renal insufficiency
Renal insufficiency	Cardiac disease
Cardiac disease	Hyperlipidemia (?)
Hyperlipidemia	Genetics (Burmese cat)
	Immune-mediated insulitis (?)

Type 2 Diabetes Mellitus

In humans, type 2 diabetes mellitus is an obesity-associated disease characterized by insulin resistance, loss of beta cell function with or without loss of beta cell mass, impaired insulin secretion, and defects in insulin receptor function and insulin receptor-signal transduction (Porte, 1990; Haataja et al, 2008; Poitout and Robertson, 2008). Humans with type 2 diabetes are typically not dependent on insulin to control the disease. Control of the diabetic state is usually possible through diet, exercise, and oral hypoglycemic drugs—hence the term *non-insulin-dependent diabetes mellitus (NIDDM).* However, insulin treatment may be necessary in some

TABLE 6-2 **BREEDS WITH A SIGNIFICANTLY ($P < 0.05$) DECREASED OR INCREASED RISK OF DIABETES MELLITUS (VETERINARY MEDICAL DATA BASE, 1970-1999)**

BREED	CASES	CONTROL	ODDS RATIO
Australian Terrier	37	1	32.10
Standard Schnauzer	105	19	4.78
Samoyed	175	45	3.36
Miniature Schnauzer	624	172	3.13
Fox Terrier	91	26	3.02
Keeshond	57	20	2.45
Bichon Frise	50	18	2.40
Finnish Spitz	35	13	2.32
Cairn Terrier	67	28	2.07
Miniature Poodle	737	356	1.79
Siberian Husky	80	45	1.53
Toy Poodle	208	139	1.29
Mixed breed	**1860**	**1609**	**1.00 (Reference)**
Beagle	73	94	0.67
English Setter	30	42	0.61
Labrador Retriever	246	364	0.58
Basset Hound	33	50	0.57
Dalmatian	28	45	0.53
Doberman Pinscher	109	182	0.51
Irish Setter	68	121	0.48
Boston Terrier	31	68	0.39
Shih Tzu	31	69	0.38
Brittany	28	64	0.37
Old English Sheepdog	14	35	0.35
Norwegian Elkhound	10	26	0.33
Golden Retriever	108	294	0.31
English Pointer	11	36	0.26
Cocker Spaniel	90	307	0.25
Great Dane	15	54	0.24
Bulldog	7	26	0.23
Shetland Sheepdog	29	107	0.23
Collie	25	109	0.19
Pekingese	14	66	0.18
German Shepherd	70	365	0.16
Airedale Terrier	8	45	0.15
German Short-Hair Pointer	6	37	0.14
Boxer	7	82	0.07

The Veterinary Medical Data Base comprises medical records of 24 veterinary schools in the United States and Canada.

From Guptill L, et al.: Time trends and risk factors for diabetes mellitus in dogs: analysis of veterinary medical data base records (1970-1999), *Vet J* 165:240, 2003. Breeds were included in the analysis if there were at least 25 cases or 25 controls.

type 2 diabetics if insulin resistance, beta cell dysfunction, or both are severe. As such, humans with type 2 diabetes may be non-insulin dependent or insulin dependent depending on the severity of abnormalities affiliated with the disease. Obesity-associated diabetes also occurs in the cat and resembles type 2 diabetes mellitus in humans (Appleton et al, 2001; see Chapter 7).

Obesity-induced insulin resistance has been documented in dogs, but progression to type 2 diabetes does not occur (Verkest et al, 2012). Studies suggest that at least some of the etiopathogenic mechanisms responsible for development of obesity-associated type 2 diabetes in humans and cats do not occur in dogs. For example, beta-cell sensitivity to changes in glucose and the first-phase of the insulin secretory response by the beta cell are lost in humans and cats but not in dogs despite years of obesity-induced insulin resistance and compensatory hyperinsulinemia (Verkest et al, 2011a). In humans, loss of the first phase of insulin secretion is an important early marker of beta-cell failure (Gerich, 2002).

Islet amyloid polypeptide (amylin) forms toxic intracellular oligomers in beta cells in humans and cats but not in dogs, and amylin does not aggregate extracellularly as histologically visible amyloid in the pancreatic islets in dogs (Haataja et al, 2008; Scheuner and Kaufman, 2008). Circulating concentrations of the adipocyte-secreted hormone adiponectin are decreased in obese humans and low adiponectin concentrations predict progression to type 2 diabetes in humans (Li et al, 2009). In contrast, circulating adiponectin concentrations were not lower in chronically obese dogs compared with lean dogs, and adiponectin was not associated with insulin sensitivity in obese dogs (Verkest et al, 2011b). Although adiponectin does not appear to play a role in the development of canine obesity-associated insulin resistance, adiponectin receptors are present on pancreatic beta-cells, and adiponectin has been shown to protect beta-cells against fatty acid-induced apoptosis (Kharroubi et al, 2003; Rakatzi et al, 2004).

Other Specific Types and Diabetic Remission

The occurrence of diabetic remission after initiating insulin therapy is uncommon in the dog despite the presence of circulating C-peptide in a small percentage of dogs at the time diabetes is diagnosed (Montgomery et al, 1996; Fall et al, 2008a; German et al, 2009; Pöppl et al, 2013; Fig. 6-1). C-peptide is the connecting peptide found in the proinsulin molecule, is secreted into the circulation in equimolar concentrations as insulin, and is a marker for functional beta cells. The presence of circulating C-peptide suggests the presence of functional beta cells. Unfortunately, in our experience, these dogs have required insulin to control hyperglycemia, suggesting the increased C-peptide concentrations in these dogs is most likely due to residual beta-cell function in dogs with type 1 diabetes mellitus rather than a severe form of type 2 diabetes.

A transient increase in endogenous insulin secretion and reduced insulin dosage requirements may occur during the initial weeks to months after the diagnosis of type 1 diabetes mellitus in humans; this is called the *honeymoon period* (Rossetti et al, 1990). A syndrome similar to the honeymoon period occurs in some newly diagnosed diabetic dogs and is characterized by excellent glycemic control using dosages of insulin considerably less than what would be expected (i.e., less than 0.2 U/kg per injection; Fig. 6-2). Presumably, the existence of residual beta-cell function when diabetes is diagnosed (see Fig. 6-1) and possible correction of glucose toxicity (see Chapter 7) after initiating insulin therapy accounts for the initial ease of treating the diabetic state. Continuing progressive destruction of residual functioning beta cells results in worsening loss of endogenous insulin

secretory capacity and a greater need for exogenous insulin to control the diabetes. As a result, glycemic control becomes more difficult to maintain, and insulin dosages increase to more commonly required amounts (0.5 to 1.0 U/kg per injection). This increase in insulin requirements usually occurs within the first 6 months of treatment.

When diabetic remission occurs, it is usually in older female dogs that are diagnosed with diabetes during diestrus or pregnancy when serum progesterone and growth hormone concentrations are increased (Fall et al, 2008b; 2010; Mared et al, 2012). Diabetic remission may also occur in spayed females with ovarian remnant syndrome and in diestrual bitches with concurrent pyometra (Pöppl et al, 2013). Documenting increased baseline serum insulin concentration supports the presence of functional beta cells and concurrent insulin resistance. Documenting an increase in serum progesterone concentration (2 ng/mL or higher) confirms the presence of functional corpora lutea and diestrus, regardless of the presence or absence of owner observed signs of a recent heat cycle. These dogs presumably have an adequate mass of functional beta cells to maintain carbohydrate tolerance when insulin resistance is not present (e.g., during anestrus), but they are unable to secrete an adequate amount of insulin to maintain euglycemia in the presence of insulin antagonism (Fall et al, 2008a). Early recognition and correction of the insulin resistance (e.g., following ovariohysterectomy) while some beta-cell function is still present may reestablish euglycemia without the long-term need for insulin therapy (Fig. 6-3). Failure to quickly correct insulin resistance often results in progressive loss of beta cells and a greater likelihood for permanent insulin dependency to control hyperglycemia (Fall et al, 2010). Bitches that have undergone diabetic remission following diestrus have a high likelihood of developing permanent insulin dependent diabetes during the next estrus. For this reason, all female dogs that develop diabetes during diestrus should be spayed as soon as possible after diabetes is diagnosed.

A similar sequence of events may occur with the administration of insulin antagonistic drugs, most notably glucocorticoids and progestogens, and other insulin resistant disorders such as hyperadrenocorticism. Resolution of hyperglycemia is most likely to occur when the hyperglycemia is mild (less than 160 mg/dL; 9 mmol/L) and has not yet resulted in glycosuria. Dogs that become euglycemic after correction of insulin resistance presumably do not have a normal population of functional beta cells, should be considered subclinical diabetics, and may or may not progress to an insulin-requiring diabetic state in the future. Treatment with insulin antagonistic drugs should be avoided, and disorders causing insulin resistance should be treated quickly to prevent overt diabetes mellitus from developing.

PATHOPHYSIOLOGY

Diabetes mellitus results from a relative or absolute deficiency of insulin secretion by the beta cells. Insulin deficiency, in turn, causes decreased tissue utilization of glucose, amino acids, and fatty acids, accelerated hepatic glycogenolysis and gluconeogenesis, and accumulation of glucose in the circulation, causing hyperglycemia. As the blood glucose concentration increases, the ability of the renal tubular cells to resorb glucose from the glomerular ultrafiltrate

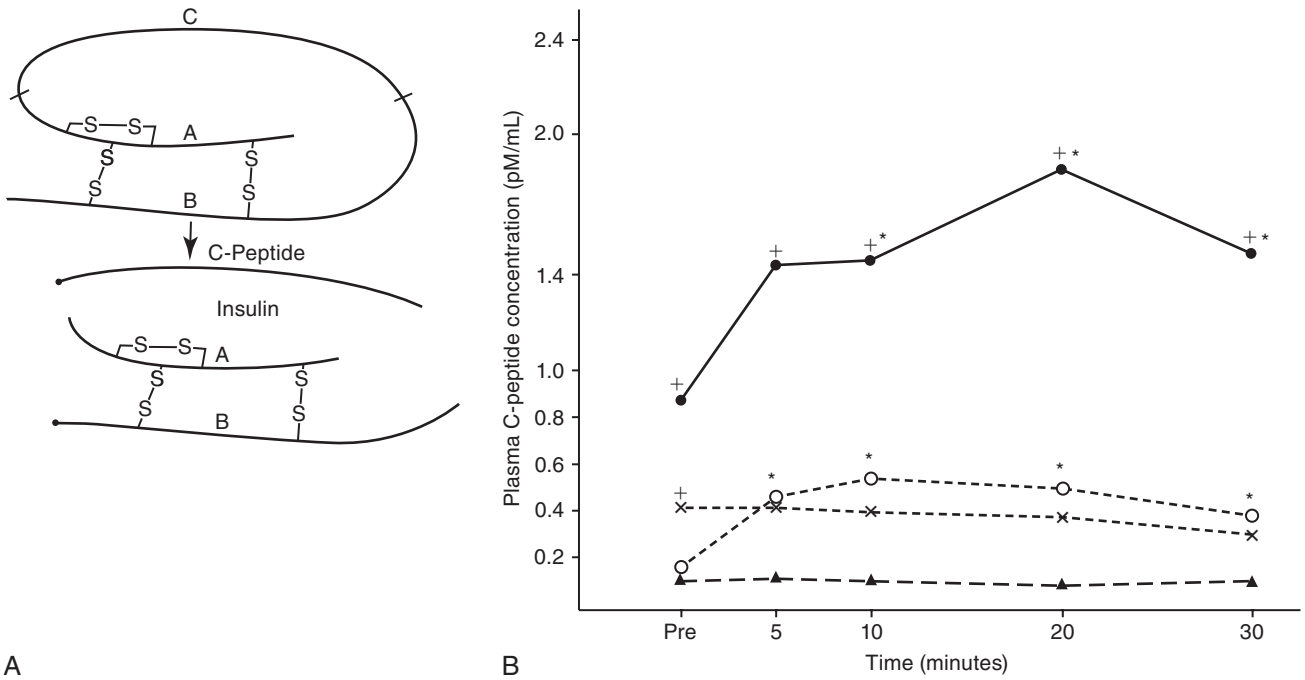

FIGURE 6-1 **A,** Schematic of the conversion of proinsulin *(top)* to insulin. Proteolytic cleavage of proinsulin forms equimolar concentrations of connecting peptide (C-peptide) and insulin, which are stored in secretory granules of beta cells. **B,** Mean plasma C-peptide concentration prior to and after intravenous (IV) administration of 1 mg glucagon in 24 healthy dogs *(broken line—open circles),* 35 dogs with diabetes mellitus and low baseline C-peptide concentration *(broken line—triangles),* 7 dogs with diabetes mellitus and increased baseline C-peptide concentration *(broken line—Xs),* and 8 dogs with naturally acquired hyperadrenocorticism *(solid line—solid circles).* (**B,** From Nelson RW: Diabetes mellitus. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 4, Philadelphia, 1995, WB Saunders Co, p. 1511.) * = significantly ($P < 0.05$) different from baseline value; + = significantly ($P < 0.05$) different from corresponding time in healthy dogs.

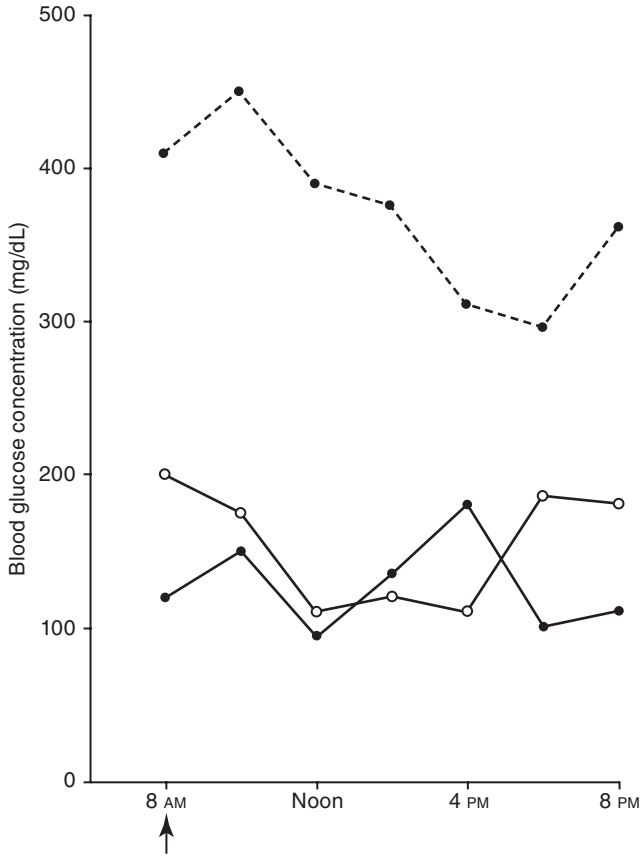

FIGURE 6-2 Blood glucose curve in a 32 kg male dog receiving 0.3 U/kg subcutaneously beef/pork source neutral protamine Hagedorn (NPH) insulin *(solid line—solid circles).* The blood glucose curve was obtained shortly after initiating insulin therapy. Five months later, glycemic control deteriorated and clinical signs recurred despite increasing the insulin dosage to 0.6 U/kg *(broken line—solid circles).* The dog was referred for possible insulin resistance. Insulin underdosage was pursued initially, and glycemic control was reestablished at an insulin dosage of 1.0 U/kg *(solid line—open circles).* ↑ = insulin injection and food.

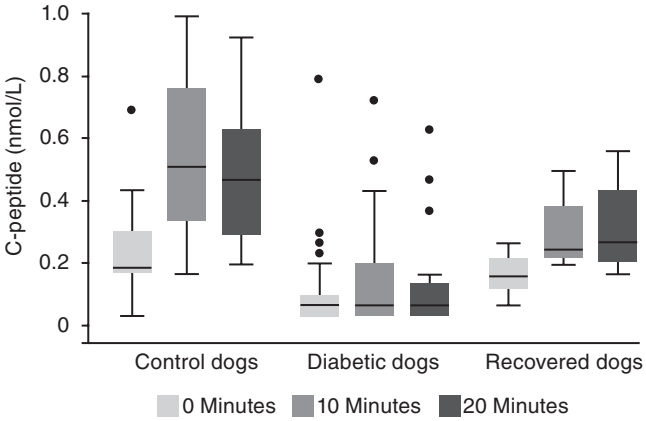

FIGURE 6-3 Box plots of the serum concentration of C-peptide before (0 minutes) and 10 and 20 minutes after the intravenous (IV) administration of a bolus dose of glucagon to 20 healthy dogs, 27 diabetic dogs, and 4 dogs that had recovered from diabetes. The *horizontal line* represents the median, the box represents the interquartile range (i.e., 25% to 75%), the *T-bars* represent the main body of data, and the *circles* represent outliers. (From Fall T, et al.: Glucagon stimulation test for estimating endogenous insulin secretion in dogs, *Vet Rec* 163:266, 2008.)

is exceeded, resulting in glycosuria. In dogs, this typically occurs whenever the blood glucose concentration exceeds 180 to 220 mg/dL (10 to 12 mmol/L). The threshold for glucose resorption appears more variable in cats, ranging from 200 to 280 mg/dL (11 to 16 mmol/L). Glycosuria creates an osmotic diuresis, causing polyuria. Compensatory polydipsia prevents dehydration. The diminished peripheral tissue utilization of ingested glucose results in weight loss as the body attempts to compensate for perceived "starvation."

The interaction of the "satiety center" in the ventromedial region of the hypothalamus with the "feeding center" in the lateral region of the hypothalamus is responsible for controlling the amount of food ingested (Barrett et al, 2012). The feeding center, responsible for evoking eating behavior, is chronically functioning but can be transiently inhibited by the satiety center after food ingestion. The amount of glucose entering the cells in the satiety center directly affects the feeling of hunger; the more glucose that enters these cells, the less the feeling of hunger and vice versa (Barrett et al, 2012). The ability of glucose to enter the cells in the satiety center is mediated by insulin. In diabetics with a relative or absolute lack of insulin, glucose does not enter satiety center cells, resulting in failure to inhibit the feeding center. Thus these individuals become polyphagic despite hyperglycemia.

The four classic signs of diabetes mellitus are polyuria, polydipsia, polyphagia, and weight loss. The severity of these signs is directly related to the severity of hyperglycemia. As these signs become obvious to the owner, the pet is brought to the veterinarian for care. Unfortunately, some dogs and cats are not identified by their owners as having signs of disease, and these untreated animals may ultimately develop diabetic ketoacidosis (DKA), systemic signs of illness, and potentially life-threatening derangements in fluid and acid/base balance. See Chapter 8 for a detailed discussion of the pathophysiology of DKA.

SIGNALMENT

Most dogs are 5 to 15 years old at the time diabetes mellitus is diagnosed (Table 6-3; Guptill et al, 2003). Juvenile-onset diabetes occurs in dogs younger than 1 year of age and is uncommon. One large epidemiologic study involving 6807 diabetic dogs and 6807 matched controls in the United States and Canada identified the following: female dogs were at increased risk for diabetes compared with male dogs, neutered male dogs were at increased risk compared with intact male dogs, mixed-breed dogs were at increased risk compared with pure breeds, and dogs weighing less than 22.7 kg were at increased risk compared with larger dogs (Guptill et al, 2003). A seasonal pattern in prevalence of diabetes was not identified. Breeds with a significantly increased or decreased risk for developing diabetes are listed in Table 6-2. Breed popularity and regions of the world may also impact breed predispositions. For example, breeds with the highest risk for diabetes in Italy include the Irish Setter, Poodle, Yorkshire Terrier, and English Setter (Fracassi et al, 2004). In Sweden, high risk breeds included Spitz type breeds (Samoyed, Swedish Elkhound, and Swedish Lapphund) and Scandinavian hound dogs (Finnish Hound, Hamilton Hound, and Drever) (Fall et al, 2007).

ANAMNESIS

The history in virtually all diabetic dogs includes the classic signs of polydipsia, polyuria, polyphagia, and weight loss. Owners will often bring their dog to the veterinarian because the dog can no longer make it through the night without having to be let outside to urinate or it begins urinating in the home. Occasionally an owner brings in

a dog because of sudden blindness caused by cataract formation (Fig. 6-4). The classic signs of diabetes mellitus may have gone unnoticed or been considered irrelevant by the owner. If the clinical signs associated with uncomplicated diabetes are not observed by the owner and impaired vision caused by cataracts does not develop, a diabetic dog is at risk for the development of systemic signs of illness (i.e., lethargy, anorexia, vomiting, and weakness) as progressive ketonemia and metabolic acidosis develop. The time sequence from the onset of initial clinical signs to the development of DKA is unpredictable, ranging from days to weeks; an onset that is somewhat dependent on the type and severity of concurrent disease causing insulin resistance and accelerating the production of ketone bodies.

A complete history is extremely important even in the "obvious" diabetic dog to explore for concurrent disorders, which are almost always present at the time diabetes mellitus is diagnosed. The clinician should always ask, "Why has the dog developed clinical signs of diabetes now?" In many dogs the insulin antagonism caused by concurrent disorders (e.g., pancreatitis, bacterial infections, recent estrus, chronic kidney disease [CKD], or hyperadrenocorticism) is the final insult leading to overt diabetes. Identification and treatment of concurrent disorders plays an integral role in the successful management of the diabetic dog, and a thorough history is the first step toward identification of these disorders.

TABLE 6-3 **AGE AT TIME OF DIAGNOSIS OF DIABETES MELLITUS IN 6807 DOGS IDENTIFIED BETWEEN JANUARY 1, 1970, AND DECEMBER 31, 1999**

AGE (YEARS)	NUMBER OF DOGS	PERCENT OF DOGS
< 1	154	2.2%
1 to 2	46	0.7%
3 to 4	195	2.8%
5 to 7	1058	15.4%
8 to 10	2543	37.1%
11 to 15	2690	39.2%
> 15	121	1.8%

From Guptill L, et al.: Time trends and risk factors for diabetes mellitus in dogs: analysis of veterinary medical data base records (1970-1999), *Vet J* 165:240, 2003.

PHYSICAL EXAMINATION

Performance of a thorough physical examination is imperative in any dog suspected of having diabetes mellitus, in part, because of the high prevalence of concurrent disorders that can affect response to treatment. The physical examination findings in a dog with newly-diagnosed diabetes depend on whether DKA is present and its severity, on the duration of diabetes prior to its diagnosis, and on the nature of any other concurrent disorder. The nonketotic diabetic dog has no classic physical examination findings. Many diabetic dogs are obese but are otherwise in good physical condition. Dogs with prolonged untreated diabetes may have lost weight but are rarely emaciated unless concurrent disease (e.g., inflammatory bowel disease, pancreatic exocrine insufficiency) is present. Lethargy may be evident. The hair coat in newly-diagnosed or poorly-controlled diabetic dogs may be sparse; the hairs dry, brittle, and lusterless; and scales from hyperkeratosis may be present. Diabetes-induced hepatic lipidosis may cause hepatomegaly. Lenticular changes consistent with cataract formation are another common clinical finding in diabetic dogs. Anterior uveitis and keratoconjunctivitis sicca may also be present. In contrast to diabetic cats, clinical signs suggestive of diabetic neuropathy (e.g., rear limb weakness, ataxia) are uncommon in newly-diagnosed diabetic dogs. Additional abnormalities may be identified in the ketoacidotic diabetic.

ESTABLISHING THE DIAGNOSIS OF DIABETES MELLITUS

A diagnosis of diabetes mellitus requires the presence of appropriate clinical signs (i.e., polyuria, polydipsia, polyphagia, weight loss) and documentation of persistent fasting hyperglycemia and glycosuria. Measurement of the blood glucose concentration using a portable blood glucose monitoring (PBGM) device (see Serial Blood Glucose Curve) and testing for the presence of glycosuria using urine reagent test strips (e.g., KetoDiastix) allows the rapid confirmation of diabetes mellitus. The concurrent documentation of ketonuria establishes a diagnosis of diabetic ketosis or ketoacidosis.

It is important to document both persistent hyperglycemia and glycosuria to establish a diagnosis of diabetes mellitus. Hyperglycemia without glycosuria does not cause polyuria and polydipsia and may occur with causes of hyperglycemia that do not typically progress to a clinical diabetic state (Box 6-1). Glycosuria without

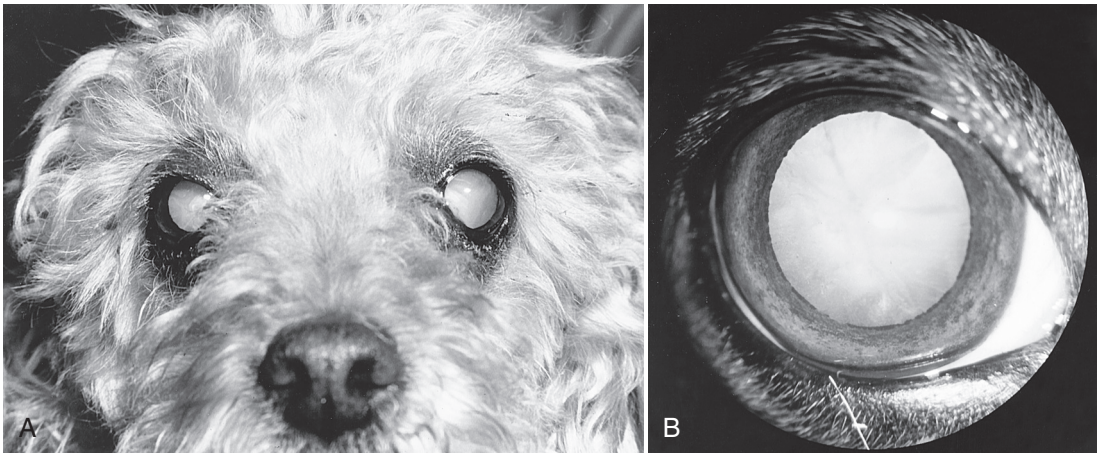

FIGURE 6-4 A, Bilateral cataracts causing blindness in a diabetic dog. **B,** Mature cataract with suture lines in a diabetic Collie.

hyperglycemia supports primary renal glycosuria or other renal tubular disorders, not diabetes mellitus.

Documenting an increase in the serum fructosamine concentration supports the presence of sustained hyperglycemia; however, a serum fructosamine concentration in the upper range of normal can occur in symptomatic diabetic dogs if the diabetes developed shortly before presentation of the dog to the veterinarian.

Mild hyperglycemia (i.e., 130 to 180 mg/dL; 7.3 to 10 mmol/L) is clinically silent and is usually an unexpected and unsuspected finding. If the dog with mild hyperglycemia is examined for polyuria and polydipsia, a disorder other than clinical diabetes mellitus should be sought. Mild hyperglycemia can occur shortly after consuming large quantities of easily digestible carbohydrates; in "stressed," hyperactive, aggressive, or extremely nervous dogs; in the early stages of development of diabetes mellitus (i.e., subclinical diabetes); and with disorders and drugs causing insulin resistance, most notably hyperadrenocorticism, glucocorticoids, and during diestrus in older intact female dogs. A diagnostic evaluation for disorders causing insulin resistance is indicated if mild hyperglycemia persists in the fasted, unstressed dog (see Concurrent Disorders Causing Insulin Resistance). Insulin therapy is usually not indicated in these animals, although some clinicians will initiate low-dose insulin therapy while searching for and treating the underlying cause of the insulin resistance in the hope that improving hyperglycemia will decrease the demand for insulin production and secretion by the beta cells and minimize further damage to the cells.

BOX 6-1 Etiologic Classification of Diabetes Mellitus and Hyperglycemia

1. Type 1 diabetes mellitus
2. Type 2 diabetes mellitus
3. Other specific types
   - A. Genetic defects
   - B. Disease of the exocrine pancreas
     - Pancreatitis
     - Exocrine pancreatic neoplasia
   - C. Endocrinopathies
     - Hyperadrenocorticism
     - Acromegaly (cat)
     - Pheochromocytoma (dog)
     - Hyperthyroidism (cat)
   - D. Drug or chemical induced
     - Glucocorticoids
     - Progestagens
     - Thyroid hormone
     - Thiazide diuretics
     - Beta adrenergic agonists
   - E. Infections
     - Pyometra
4. Gestational diabetes mellitus
   - A. Diestrus (bitch)
   - B. Ovarian remnant syndrome
5. Miscellaneous causes of hyperglycemia
   - A. Head trauma
   - B. Critical illness
   - C. Stress, aggression, fright (cat)
   - D. Dextrose-containing fluids
   - E. Parenteral nutrition solutions
   - F. Postprandial

Modified from the American Diabetes Association etiologic classification for humans.

CLINICAL PATHOLOGIC ABNORMALITIES

Overview of Patient Evaluation

A thorough clinicopathologic evaluation is recommended once the diagnosis of diabetes mellitus has been established. The clinician must be aware of any disease that may be causing or contributing to the carbohydrate intolerance (e.g., hyperadrenocorticism), that may result from the carbohydrate intolerance (e.g., bacterial cystitis), or that may mandate a modification of therapy (e.g., pancreatitis) (Hess et al, 2000b; Peikes et al, 2001). The minimum laboratory evaluation in any newly-diagnosed diabetic dog should include a complete blood count (CBC), serum biochemical panel, and urinalysis with bacterial culture. Serum progesterone concentration should be determined if diabetes mellitus is diagnosed in an intact bitch, regardless of her cycling history. If available, abdominal ultrasound is indicated to assess for pancreatitis, adrenomegaly, pyometritis in an intact bitch, and abnormalities affecting the liver and urinary tract (e.g., changes consistent with pyelonephritis or cystitis). Because of the relatively high prevalence of pancreatitis in diabetic dogs, measurement of pancreatic lipase immunoreactivity (cPLI) should be considered, especially if abdominal ultrasound is not available. Additional tests may be warranted after obtaining the history, performing the physical examination, or identifying ketonuria. The laboratory evaluation of dogs with glycosuria and ketonuria is discussed in detail in Chapter 8. Potential clinical pathologic abnormalities are listed in Box 6-2.

BOX 6-2 Clinicopathologic Abnormalities Commonly Found in Dogs and Cats with Uncomplicated Diabetes Mellitus

Complete Blood Count
Typically normal
Neutrophilic leukocytosis, toxic neutrophils if pancreatitis or infection present

Biochemistry Panel
Hyperglycemia
Hypercholesterolemia
Hypertriglyceridemia (lipemia)
Increased alanine aminotransferase activity (typically < 500 U/L)
Increased alkaline phosphatase activity (typically < 500 U/L)

Urinalysis
Urine specific gravity (typically > 1.025)
Glycosuria
Variable ketonuria
Proteinuria
Bacteriuria

Ancillary Tests
Hyperlipasemia (canine pancreatic-specific lipase [cPL]) if pancreatitis present
Hyperamylasemia if pancreatitis present
Serum trypsin-like immunoreactivity (TLI) usually normal
- Low with pancreatic exocrine insufficiency
- High with acute pancreatitis
- Normal to high with chronic pancreatitis

Variable serum baseline insulin concentration
- Type 1 diabetes: Low, normal
- Type 2 diabetes: Low, normal, increased
- Insulin resistance induced: Low, normal, increased

Complete Blood Count

Results of a CBC are usually normal in the uncomplicated diabetic dog. A mild polycythemia may be present if the dog is dehydrated. An elevation of the white blood cell count may be caused by either an infectious or inflammatory disorder, such as pancreatitis. The presence of toxic or degenerative neutrophils or a significant shift toward immaturity of the cells supports the presence of an infectious process or severe necrotizing pancreatitis as the cause of the leukocytosis.

Serum Biochemical Panel

The prevalence and severity of abnormalities identified in the serum biochemistry panel are dependent on the duration of untreated diabetes and the presence of concurrent disease, most notably pancreatitis (Hess et al, 2000b). The serum biochemical panel is often unremarkable in "healthy" diabetic dogs without significant concurrent disease, aside from hyperglycemia and hypercholesterolemia. The most common abnormalities are an increase in serum alanine aminotransferase and alkaline phosphatase activities and hypercholesterolemia (see later). The increase in liver enzyme activities in "healthy" diabetic dogs is usually mild (less than 500 U/L) and presumed to be a result of hepatic lipidosis. Serum alkaline phosphatase activities in excess of 800 U/L should raise suspicion for concurrent hyperadrenocorticism, especially if other abnormalities consistent with hyperadrenocorticism are identified in the laboratory data (see Chapter 10). Serum alanine aminotransferase activities in excess of 600 U/L should raise suspicion for hepatopathy other than hepatic lipidosis, especially if additional abnormalities in endogenous liver function tests (e.g., low urea nitrogen, hypoalbuminemia, or increased serum bile acids) are identified. An increase in the serum total bilirubin concentration should raise suspicion for extrahepatic biliary obstruction caused by concurrent pancreatitis. When appropriate, abdominal ultrasound and histologic evaluation of a liver biopsy specimen may be indicated to establish concurrent liver disease.

The blood urea nitrogen (BUN) and serum creatinine concentrations are usually normal in the uncomplicated diabetic. An elevation in these parameters may be due to either primary renal failure or prerenal uremia secondary to dehydration. Primary renal failure as a result of glomerulosclerosis, which is damage specifically related to chronic hyperglycemia, is a well-recognized complication in humans but is uncommon in dogs (see Diabetic Nephropathy). Evaluation of urine specific gravity should help differentiate primary renal failure from prerenal uremia. Remember to consider the impact of glycosuria on results of urine specific gravity determined by refractometry (see later).

Alterations in serum electrolytes and acid-base parameters are common in dogs with DKA and are discussed in Chapter 8.

Urinalysis

Abnormalities identified in the urinalysis that are consistent with diabetes mellitus include glycosuria, ketonuria, proteinuria, and bacteriuria with or without associated pyuria and hematuria. The dog with uncomplicated diabetes usually has glycosuria without ketonuria. However, a relatively healthy diabetic may also have trace to small amounts of ketones in the urine. If large amounts of ketones are present in the urine—especially in an animal with systemic signs of illness (e.g., lethargy, vomiting, or dehydration), a diagnosis of DKA should be made and the animal treated appropriately.

The presence and severity of glycosuria should be considered when interpreting the urine specific gravity. Despite polyuria and polydipsia, urine specific gravities typically range from 1.025 to 1.035 in untreated diabetic dogs, in part, because of the large amount of glucose in the urine. In general, 2% or 4+ glycosuria as measured on urine reagent test strips will increase the urine specific gravity 0.008 to 0.010 when urine specific gravity is measured by refractometry. As such, identification of a urine specific gravity less than 1.020 in combination with 2% glycosuria suggests a concurrent polyuric/polydipsic disorder, most notably hyperadrenocorticism or CKD.

Proteinuria may be the result of urinary tract infection or glomerular damage secondary to disruption of the basement membrane (Struble et al, 1998). Identification of pyuria, hematuria, and bacteriuria suggests the presence of a urinary tract infection. However, failure to identify pyuria and hematuria does not rule out urinary tract infection (McGuire et al, 2002). Because of the relatively high prevalence of concurrent urinary tract infections in diabetic dogs, urine obtained by antepubic cystocentesis using aseptic technique should be submitted for bacterial culture and antibiotic sensitivity testing in all dogs with newly-diagnosed diabetes mellitus, regardless of the findings on urinalysis (Hess et al, 2000b).

Serum Cholesterol and Triglyceride Concentrations

Serum cholesterol and triglyceride concentrations are typically increased in newly-diagnosed diabetic dogs. Insulin is a powerful inhibitor of lipolysis and free fatty acid oxidation. During a state of insulin deficiency, lipoprotein lipase activity is reduced, hormone-sensitive lipase is activated, hepatic production of triglyceride-rich very–low-density lipoprotein (VLDL) particles is increased, and clearance of VLDL particles is decreased (Eckel, 1989; Massillon et al, 1997; Semenkovich et al, 2011). Activation of hormone-sensitive lipase results in the release of large quantities of free fatty acids from adipocytes into the blood. These free fatty acids are ultimately converted by the liver into triglycerides, packaged into VLDL particles, and secreted back into the circulation. Increased intrahepatic cholesterol concentration down-regulates the hepatocyte low-density lipoprotein (LDL) receptor, consequently reducing the clearance of circulating cholesterol-containing LDL and high-density lipoprotein (HDL) particles, which in turn causes hypercholesterolemia.

Chylomicrons and VLDLs are primarily involved in triglyceride metabolism, whereas HDLs and LDLs are primarily involved in cholesterol metabolism. In diabetic humans, circulating concentrations of LDLs and HDLs are increased and decreased, respectively. The combination of high LDL and low HDL cholesterol concentrations may play a role in the accelerated development of atherosclerotic vascular disease and coronary heart disease, which is the major long-term complication of diabetes in humans (Garg and Grundy, 1990). Similar vascular complications have been infrequently documented in diabetic dogs (Hess et al, 2002), presumably because HDLs predominate in dogs (as opposed to LDLs in humans), and dogs have a shorter life span that may limit development of atherosclerosis (Bauer, 2004). Fortunately, most lipid derangements in diabetic dogs can be improved with insulin and dietary therapy.

Pancreatic Enzymes

Blood tests to assess for the presence of pancreatitis should always be considered in the newly-diagnosed diabetic dog, especially if

abdominal ultrasound is not available. Measurement of canine pancreatic-specific lipase (cPL) is currently the blood test of choice for identifying pancreatitis (Trivedi et al, 2011; McCord et al, 2012). Sensitivity and specificity of cPL varies between studies and is dependent on the severity of pancreatitis and the cutoff value (200 versus 400 μg/L) used to separate normal from pancreatitis (McCord et al, 2012; Bostrom et al, 2013). Serum cPL concentrations can be increased in dogs with a histologically confirmed normal pancreas and normal in dogs with histologically confirmed inflammation of the pancreas, especially when the inflammatory process is chronic and mild (Forman et al, 2004; Trivedi et al, 2011). Interpretation of serum cPL results should always be done in context with the history, physical examination findings, and additional findings on the laboratory tests. In our experience, abdominal ultrasound is the single best diagnostic test for identifying acute and chronic pancreatitis in the dog; however, results are equipment and operator dependent. Nevertheless, abdominal ultrasound should be considered if pancreatitis is suspected after evaluation of the history, physical examination, and laboratory test results. The concomitant presence of pancreatitis may necessitate the instigation of intensive fluid therapy and the initiation of diets aimed at treating pancreatitis rather than diabetes. Identification of chronic pancreatitis also has important prognostic implications regarding success of establishing and maintaining control of glycemia and long-term survival.

Measurement of serum trypsin-like immunoreactivity (TLI) is no longer recommended for identifying pancreatitis but is currently the blood test of choice to diagnose exocrine pancreatic insufficiency; an uncommon complication of diabetes mellitus that presumably develops as a sequela of chronic pancreatitis in most diabetic dogs (Wiberg et al, 1999; Wiberg and Westermarck, 2002). Exocrine pancreatic insufficiency should be suspected in diabetic dogs that are difficult to regulate with insulin, are thin or emaciated despite polyphagia, and defecate increased amounts of soft stools—not the voluminous, rancid stools considered classic for exocrine pancreatic insufficiency (EPI). Mild diffuse thickening of the small intestine may be evident during abdominal palpation. Serum TLI should be less than 2.5 μg/L in diabetic dogs with concurrent exocrine pancreatic insufficiency.

Serum Thyroxine Concentration

The veterinarian may periodically have to interpret a serum thyroxine (T_4) concentration in a diabetic dog, either because serum T_4 is a routine part of the serum biochemistry panel; because hypothyroidism is suspected after a review of the history, clinical signs, and physical examination findings; or because severe hyperlipidemia is identified or as part of the diagnostic evaluation for insulin resistance (Hofer-Inteeworn et al, 2012). Interpretation of serum T_4 results must be done cautiously, especially in a dog with newly-diagnosed diabetes mellitus and concurrent illness, such as pancreatitis or infection. "Healthy" diabetic dogs without concurrent illness usually have normal serum T_4 concentrations. However, the more poorly controlled the diabetic state and the more severe the concurrent illness, the more likely serum T_4 concentrations will be decreased into the hypothyroid range because of the suppressive effect of concurrent illness on the pituitary-thyroid axis rather than because of naturally-acquired hypothyroidism (see Chapter 3). As a general rule, in a newly-diagnosed diabetic dog with a concurrent low serum T_4 concentration, we treat the diabetes and reevaluate serum T_4 and thyroid-stimulating hormone (also known as thyrotropin; TSH) concentrations once control of glycemia has been established. If hypothyroidism is strongly suspected at the time diabetes is diagnosed, we will evaluate serum free T_4 and TSH concentrations before initiating sodium levothyroxine treatment. See Chapter 3 for a more detailed discussion of the effects of concurrent lipemia, illness, and drug therapy on serum thyroid hormone concentrations and the tests used to diagnose hypothyroidism in dogs.

Serum Insulin Concentration

Measurement of serum insulin concentration (either baseline or after the administration of an insulin secretagogue) is not a routine part of our diagnostic evaluation of the newly-diagnosed diabetic dog. In theory, identifying increased endogenous serum insulin concentrations in a newly-diagnosed diabetic dog would suggest the presence of functioning beta cells and the presence of an underlying insulin antagonistic disorder. However, because the vast majority of dogs with newly-diagnosed diabetes have type 1 diabetes and serum insulin concentration is typically in the lower half of normal or undetectable, routine measurement of serum insulin concentration is not a cost-effective diagnostic procedure. The exceptions are older intact female dogs in diestrus and with newly-diagnosed diabetes mellitus (see Other Specific Types and Diabetic Remission). It is imperative that the insulin assay has been validated in dogs; that the reference interval has been determined using healthy, fasted dogs; and that the diabetic dog has not been recently treated with exogenous insulin. Most insulin assays will measure exogenously administered insulin, resulting in an increased serum insulin concentration and a misinterpretation of beta cell function in the diabetic dog. As a general rule, exogenous insulin should be withheld for at least 24 hours before blood is obtained for endogenous serum insulin measurement.

TREATMENT OF NONKETOTIC DIABETES MELLITUS

Goals of Therapy

There are two primary goals of therapy. The first goal is the elimination of the owner-observed signs occurring secondary to hyperglycemia and glycosuria. A persistence of clinical signs and the development of chronic complications (Table 6-4) are directly correlated with the severity and duration of hyperglycemia. Limiting blood glucose concentration fluctuations and maintaining near-normal glycemia will help minimize the severity of clinical signs and prevent the complications of poorly controlled diabetes. In the diabetic dog, this can be accomplished through proper insulin therapy, diet, exercise, and the prevention or control of concurrent inflammatory, infectious, neoplastic, and hormonal disorders.

Although it is worthwhile attempting to normalize the blood glucose concentration, the veterinarian must also guard against the animal developing of hypoglycemia, which is a serious and potentially fatal complication of therapy. Hypoglycemia is most apt to occur as the result of overzealous insulin therapy. The veterinarian must balance the benefits of tight glucose control obtainable with aggressive insulin therapy against the risk for hypoglycemia.

The second goal is to minimize the impact of therapy on the owner's lifestyle. A recent study evaluated the psychological and social impact of diabetes and its treatment on the quality of life of 101 owners of diabetic dogs living in the United Kingdom, United States, Canada, Australia, and Europe (Niessen et al, 2012). The top 10 negative impact items were associated mostly with the owner's quality of life rather than the pet's quality of

TABLE 6-4 **COMPLICATIONS OF DIABETES MELLITUS IN DOGS AND CATS**

COMMON	UNCOMMON
Iatrogenic hypoglycemia	Peripheral neuropathy (dog)
Persistent polyuria, polydipsia, weight loss	Glomerulonephropathy, glomerulosclerosis
Cataracts (dog)	Retinopathy
Bacterial infections, especially in the urinary tract	Exocrine pancreatic insufficiency
Pancreatitis	Gastric paresis
Ketoacidosis	Diabetic dermatopathy (dog) (i.e., superficial necrolytic dermatitis)
Hepatic lipidosis	
Peripheral neuropathy (cat)	

TABLE 6-5 **TOP TEN NEGATIVE PSYCHOLOGICAL AND SOCIAL IMPACTS OF DIABETES MELLITUS AND ITS TREATMENT ON THE QUALITY OF LIFE OF OWNERS OF A DIABETIC DOG**

ITEM	MEAN ITEM WEIGHTED IMPACT SCORE
Worry about pet's diabetes	-5.92
Interferes with visiting family and friends	-5.68
Worry about the dog developing cataracts	-5.58
Worry about boarding the dog	-5.18
Worry about dog developing hypoglycemia	-4.95
Having to fit the dog's needs into their social life	-4.82
Cost of treating the diabetes	-4.11
Worry about future ability to care for the dog	-4.07
Having to fit the dog's needs into their work schedule	-3.88
Restricting the owners' vacation and work activities	-3.88

Adapted from Niessen SJM, et al.: Evaluation of a quality-of-life tool for dogs with diabetes mellitus, *J Vet Intern Med* 26:953, 2012.
The quality of life survey was completed by 101 owners originating from the United Kingdom, United States, Canada, Australia, and Europe.

life (Table 6-5). The only positive items identified by the owners were related to more interactions and development of a special bond with their dog. Fortunately, 81% of diabetic dog owners rated their dog's quality of life as good despite 84% reporting a negative impact of diabetes on their dog's quality of life. Awareness of the impact of the treatment regimen, home monitoring, and frequency of evaluations by the veterinarian on the client and simplifying the overall management of the diabetic dog as much as possible without negatively impacting control of glycemia is important for the long-term success of treating diabetes.

Insulin Therapy

Overview of Insulin Preparations

Insulin preparations typically used for the home treatment of diabetes in dogs and cats include intermediate-acting insulin preparations (neutral protamine Hagedorn [NPH], Lente) and long-acting basal insulin preparations (protamine zinc insulin [PZI], insulin glargine, insulin detemir; Table 6-6). NPH (Humulin N, Novolin N) is a recombinant human insulin, Lente (Vetsulin, Caninsulin) is a purified pork-source insulin, PZI (Pro-Zinc) is a recombinant human insulin, and insulin glargine (Lantus) and insulin detemir (Levemir) are insulin analogues. NPH and PZI insulin preparations contain the fish protein protamine and zinc to delay insulin absorption and prolong the duration of insulin effect (Davidson et al, 1991). Lente insulin relies on alterations in zinc content and the size of zinc-insulin crystals to alter the rate of insulin absorption from the subcutaneous site of deposition. The larger the crystals are, the slower the rate of absorption and the longer the duration of effect. Lente insulin contains no foreign protein (i.e., protamine). Lente insulin is a mixture of three parts of short-acting, amorphous zinc insulin and seven parts of long-acting, crystalline zinc insulin. Lente insulin is considered an intermediate-acting insulin, although plasma insulin concentrations may remain increased for longer than 14 hours following subcutaneous administration in some dogs (Graham et al, 1997). The manufacturer of porcine Lente insulin now recommends vigorous shaking of the insulin vial until a homogeneous milky suspension is obtained prior to withdrawal of the insulin into the syringe.

NPH insulin, insulin glargine and insulin detemir are U100 insulin preparations (i.e., 100 units of insulin per mL of solution). Porcine-source Lente and protamine zinc insulin are approved by the Food and Drug Administration (FDA) for treatment of diabetes in dogs and cats, respectively and so are U40 insulin preparations (i.e., 40 units of insulin per mL of solution). The appropriate insulin syringe should be used for the insulin preparation being administered (i.e., U40 or U100 insulin syringe for a U40 or U100 insulin preparation). Insulin pens are also available for NPH insulin, porcine-source Lente insulin, insulin glargine, and insulin detemir.

Porcine-source Lente and recombinant human NPH insulin are effective for the treatment of diabetes in dogs (Lorenzen, 1992; Monroe et al, 2005). Problems with prolonged duration of insulin effect can occur with both insulin preparations but are not common (Hess and Ward, 2000; Fleeman et al, 2009a). Problems with short duration of insulin effect despite twice a day administration are more common than problems with prolonged duration of insulin effect, especially with NPH insulin (see Complications of Insulin Therapy; Palm et al, 2009). For this reason, porcine-source Lente insulin is considered the initial insulin of choice for the home treatment of diabetes in dogs. For a period of time, porcine-source Lente insulin was not available in the United States and veterinarians were forced to use alternative insulin preparations, most commonly NPH or insulin detemir. Fortunately porcine-source Lente insulin is once again available in the United States.

Recombinant human PZI insulin is commonly used for the treatment of diabetes in cats but published experiences with PZI in diabetic dogs is limited. In a recent study, PZI administered twice a day was effective in improving or maintaining control of glycemia in the majority of diabetic dogs enrolled in the study, and more than 80% of owners were satisfied with the results of treatment (Della-Maggiore et al, 2012). However, prolonged duration of PZI effect was a common problem that resulted in blood glucose nadirs often occurring at the beginning or end of the blood glucose cure, inconsistency in blood glucose results in

TABLE 6-6 **COMMONLY-USED INSULIN PREPARATIONS FOR TREATING DIABETES IN DOGS AND CATS**

			Administration		Typical Duration of Effect (hour)		
INSULIN	**ORIGIN**	**INDICATIONS**	**ROUTE**	**FREQUENCY**	**DOG**	**CAT**	**COMMON PROBLEMS**
Regular crystalline	Recombinant human	Treat DKA	IV	Continuous infusion	—	—	Rapid decrease in blood glucose concentration; may cause hypokalemia
			IM	Hourly initially	4-6	4-6	
			SC	Every 6 to 8 hours	6-8	6-8	
		Treat diabetes at home	SC	Every 8 hours	6-8	6-8	
Lispro	Recombinant human analog	Treat DKA	IV	Continuous infusion	—	—	Rapid decrease in blood glucose concentration; may cause hypokalemia
NPH	Recombinant human	Treat diabetes at home	SC	Every 12 hours	6-12	6-10	Short duration of effect in dogs and cats
Lente	100% pork	Treat diabetes at home; good initial insulin for dogs	SC	Every 12 hours	8-14	6-12	Short duration of effect in cats
PZI	Recombinant human	Treat diabetes at home; good initial insulin for cats	SC	Every 12 hours	10-16	10-14	Duration of effect too long for every-12-hour therapy in some dogs; unpredictable timing of glucose nadir in some dogs
Glargine	Recombinant human analog	Treat diabetes at home; good initial insulin for cats	SC	Every 12 to 24 hours	8-16	8-16	Duration of effect too long for every-12-hour therapy in some cats and dogs; weak glucose lowering effect and unpredictable timing of glucose nadir in some dogs
Detemir	Recombinant human analog	Treat diabetes at home	SC	Every 12 to 24 hours	8-16	8-16	Duration of effect too long for every-12-hour therapy in some cats and dogs; insulin dosage requirements considerably lower than with other insulin preparations

From Nelson RW, Couto CG: *Small animal internal medicine,* ed 5, St Louis, 2014, Mosby Elsevier, p. 784.
DKA, Diabetic ketoacidosis; *IM,* intramuscular; *IV,* intravenous; *NPH,* neutral protamine Hagedorn; *PZI,* protamine zinc insulin; *SC,* subcutaneous.

individual dogs, and difficulty in achieving ideal control of hyperglycemia within the time period of the study (60 days) in some dogs (Fig. 6-5). Problems with hypoglycemia and initiation of the Somogyi response may occur when an insulin preparation with a duration of effect longer than 12 hours is administered every 12 hours. Problems with prolonged duration of PZI effect precludes routine use of PZI in newly-diagnosed diabetic dogs but supports the potential use of PZI in diabetic dogs that are poorly controlled because of short duration of effect of NPH or Lente insulin.

Insulin Analogues. Recently, recombinant DNA technology has been applied for the production of insulin analogues that more closely duplicate the basal and meal-time components of endogenous insulin secretion. Rapid-acting insulin analogues include insulin lispro (Humalog), insulin aspart (Novolog) and insulin glulisine (Apidra). The relatively slow absorption of regular insulin is attributed to hexamer formation of insulin molecules that occurs when zinc is added to the solution that makes up regular insulin (Hirsch, 2005). The hexamers of insulin molecules slowly dissociate before absorption into the circulation occurs. By replacing certain amino acids in the insulin molecule, the tendency to self-associate can be reduced without affecting the insulin-receptor kinetics. Insulin lispro is produced by inverting the natural amino acid sequence of the B-chain at B28 (proline) and B29 (lysine), insulin aspart is produced by substituting aspartic acid for proline at position B28, and insulin glulisine is produced by substituting lysine for asparagine at position B3 and glutamic acid for lysine at position B29 (Lindholm et al, 2002; Home, 2012; Fig. 6-6). As a consequence of these alterations, insulin lispro, insulin aspart,

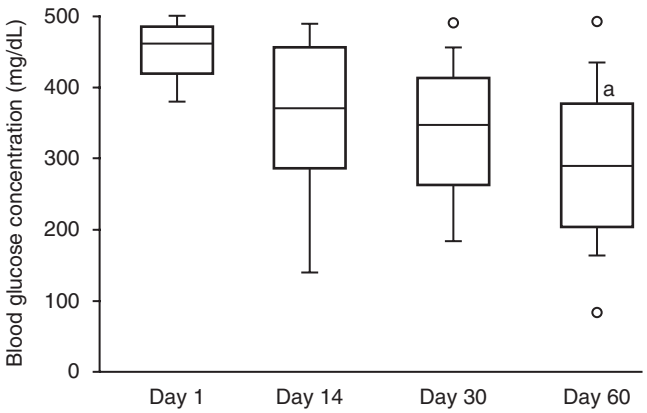

FIGURE 6-5 Box plots of the 10-hour mean blood glucose concentrations in 17 dogs with diabetes mellitus treated by the administration of various doses of recombinant human protamine zinc insulin (PZI) twice daily for 60 days. The 10-hour mean blood glucose concentration is the mean of the six blood glucose concentrations measured during a 10-hour period. The median time from insulin administration to the blood glucose nadir was 8 to 10 hours and occurred at the start or end of the 10-hour blood sampling interval in 54% of 68 blood glucose curves. The *horizontal line* represents the median, the *box* represents the interquartile range (i.e., 25% to 75%), the *T-bars* represent the main body of data, and the *circles* represent the outliers. (From Della-Maggiore A, et al.: Efficacy of protamine zinc recombinant human insulin for controlling hyperglycemia in dogs with diabetes mellitus, *J Vet Intern Med* 26:109, 2012.) *a,* P = 0.0003, compared with results on day 1.

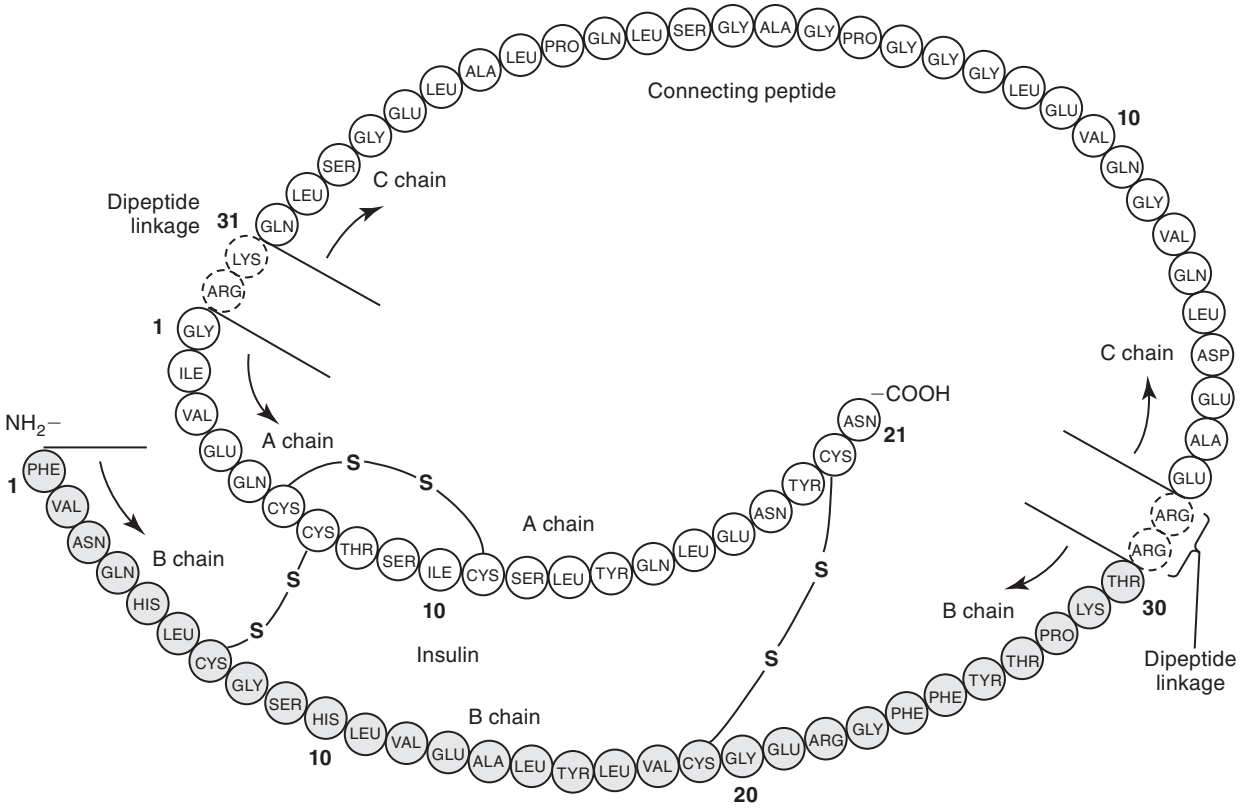

FIGURE 6-6 Amino acid structure of human proinsulin, connecting peptide (C-peptide) and insulin. The insulin molecule consists of an A and B chain connected by two disulfide bridges. (From Masharani U, Karam JH: Pancreatic hormones and diabetes mellitus. In Gardner DA, Shoback D, editors: *Greenspan's basic & clinical endocrinology,* ed 9, New York, 2011, McGraw-Hill, with permission.)

and insulin glulisine exhibit monomeric behavior in solution and display a rapid absorption, faster pharmacodynamic action, and shorter duration of effect than short-acting regular crystalline insulin (Howey et al, 1994; Home et al, 1999; Lindholm et al, 1999). Insulin lispro and insulin aspart are the current prandial insulins (i.e., insulin administered before each meal) commonly used for control of postprandial blood glucose concentrations in human diabetics and are typically administered three times a day before each of the three main meals (breakfast, lunch, and dinner). The role, if any, of these insulins for the home treatment of diabetic dogs remains to be determined. Because of their extremely short duration of effect, insulin lispro and insulin aspart would have to be used in conjunction with a longer-acting insulin preparation to maintain control of glycemia. A recent study documented similar effectiveness of insulin lispro and regular crystalline insulin for the treatment of DKA in dogs (Sears et al, 2012).

Insulin glargine (Lantus) and insulin detemir (Levemir) are long acting (basal) insulin analogues that have a slow, sustained absorption from the subcutaneous site of insulin deposition, are designed to inhibit hepatic glucose production, are typically administered once a day at bedtime, and are used in conjunction with rapid-acting (prandial) insulin analogues in diabetic humans. Insulin glargine has been modified by replacing the amino acid asparagine with glycine at position A21 of the A chain, and two arginines have been added to the C-terminus of the B chain of insulin; these modifications shift the isoelectric point from a pH of 5.4 toward a neutral pH (Pieber et al, 2000). This shift makes insulin glargine more soluble at a slightly acidic pH and less soluble at a physiological pH than native human insulin. The solution in the bottle of glargine is acidic, which keeps glargine soluble and suspended in the solution (i.e., the solution is clear, and the bottle does not need to be shaken prior to drawing up the insulin into the syringe). Because of this dependency on pH, glargine should not be diluted or mixed with anything that may change the pH of the solution. Glargine forms microprecipitates in the subcutaneous tissue at the site of injection from which small amounts of insulin glargine are slowly released and absorbed into the circulation. In humans, the slow sustained release of insulin glargine from these microprecipitates results in a relatively constant concentration/time profile over a 24-hour period with no pronounced peak in serum insulin. The glucose-lowering effect of insulin glargine is similar to that of human insulin, the onset of action following subcutaneous administration is slower than NPH insulin, and the duration of effect is prolonged compared with NPH insulin (Owens et al, 2000). Insulin glargine is currently recommended as a basal insulin (i.e., sustained long-acting insulin used to inhibit hepatic glucose production) administered once a day at bedtime and used in conjunction with either rapid-acting insulin analogs or oral hypoglycemic drugs in human diabetics (Rosenstock et al, 2000; 2001).

Insulin glargine is commonly used for the treatment of diabetes in cats, but published experiences with insulin glargine in diabetic dogs are limited. Time-action profiles performed in three healthy dogs suggested the potential for prolonged duration of action of insulin glargine, a duration that could potentially cause problems if insulin glargine is administered twice a day (Mori et al, 2008; Fig. 6-7). In a recent study, insulin glargine administered twice a day was effective in improving or maintaining control of glycemia in

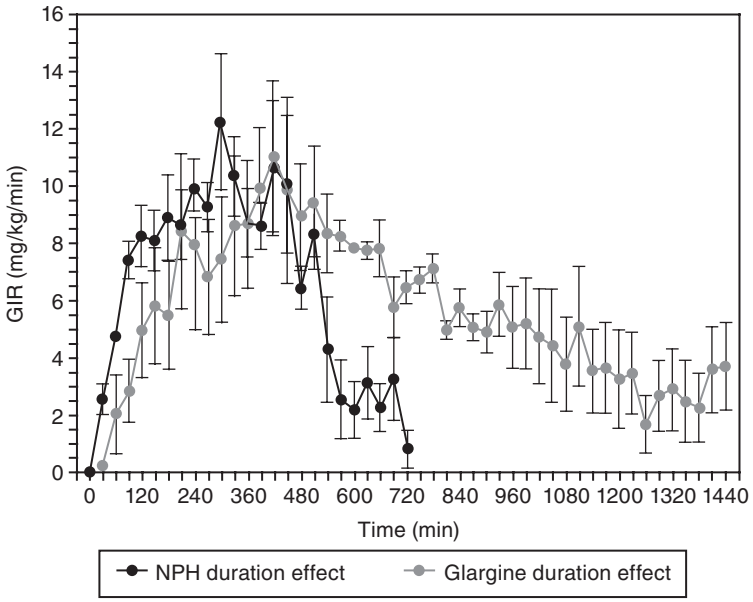

FIGURE 6-7 Time-action profile comparison between neutral protamine Hagedorn (NPH) insulin and insulin glargine for a 24-hour period. Results are presented as mean ± standard error of the mean glucose infusion rate (GIR) required to maintain euglycemia over time for three healthy non-diabetic dogs after subcutaneous (SC) administration of either 0.5 U/kg NPH insulin or 0.5 U/kg insulin glargine at time 0. Higher values of GIR indicate stronger insulin action. (Adapted from Mori A, et al.: Comparison of time-action profiles of insulin glargine and NPH insulin in normal and diabetic dogs, *Vet Res Commun* 32:563, 2008).

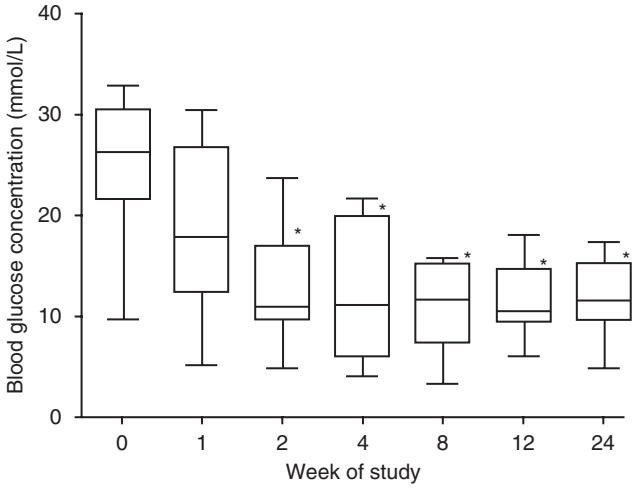

FIGURE 6-8 Box plots of 12-hour mean blood glucose concentrations in the blood glucose curves for 12 dogs with diabetes mellitus treated by various doses of insulin glargine administration twice daily for 24 weeks. Twelve-hour mean blood glucose concentration is the mean of the seven blood glucose concentrations measured during a 12-hour period. See Fig. 6-5 legend for interpretation of box plots. (From Fracassi F, et al.: Use of insulin glargine in dogs with diabetes mellitus, *Vet Rec* 170:52, 2012.) * = $P < 0.05$.

the majority of diabetic dogs enrolled in the study (Fracassi et al, 2012; Fig. 6-8). Fifty-eight (33%) of the dogs had attained good or moderate glycemic control by week 24 of the study. Insulin dosages required to attain glycemic control were similar to insulin dosages reported with NPH, Lente, and PZI insulin (Table 6-7). The timing of the glucose nadir was variable, suggesting that short and especially prolonged duration of action of insulin glargine occurs in diabetic dogs (Fig. 6-9). The authors speculated that the published success rate of other types of insulins (i.e., NPH and Lente) was somewhat better than insulin glargine. Our experiences with insulin glargine in dogs have been mixed and somewhat disappointing. We have been unable to attain good glycemic control in the majority of diabetic dogs treated with insulin glargine. We do not consider insulin glargine a first choice insulin for the treatment of diabetes in dogs, but we do consider using insulin glargine in diabetic dogs with problems of short duration of effect of NPH and Lente insulin and problems with prolonged duration of effect of insulin detemir (see Complications of Insulin Therapy).

Insulin detemir is also a long-acting basal insulin analogue, in which the amino acid threonine has been removed at B30 and a 14 carbon fatty acid (myristic acid) has been bound to the lysine amino acid at position B29 of the B chain of the insulin molecule. Prolonged action results from strong self-association of the insulin molecules and binding of insulin detemir to albumin in the subcutaneous tissues and the systemic circulation through the fatty acid chain attached to lysine at B29. Binding to albumin resulted in reduced free insulin detemir concentrations in the circulation and slower distribution of insulin to peripheral target tissues (Hamilton-Wessler et al, 1999). Insulin detemir is a clear, colorless, aqueous neutral solution that does not need to be shaken prior to drawing up the insulin into the syringe. The manufacturer recommends that insulin detemir not be mixed or diluted with other insulin preparations. Insulin detemir can be diluted using the Insulin Diluting Medium for NovoRapid (insulin aspart) and Levemir (detemir) supplied by Novo Nordisk.

Published experiences with insulin detemir in diabetic dogs are limited. A recent study would suggest that insulin detemir is currently the longest acting insulin preparation for use in diabetic dogs. Time-action profiles performed in three healthy dogs identified a prolonged duration of action of insulin detemir with peak insulin action at 8 to 12 hours after the subcutaneous administration of insulin detemir and a duration of effect in excess of 16 hours (Sako et al, 2011; Fig. 6-10). In the same study, insulin detemir was more effective in attaining glycemic control in five diabetic dogs after 5 days of treatment than NPH or insulin glargine. Insulin dosages ranged from 0.41 to 0.63 U/kg, 0.34 to 0.54 U/kg, and 0.07 to 0.23 U/kg for NPH, insulin glargine, and insulin detemir, respectively. The lower dosage requirements for insulin detemir are presumably related to the prolonged duration of insulin action combined with twice a day administration. Sako, et al., (2011) speculated that insulin detemir carries a higher risk of inducing hypoglycemia as compared to either NPH insulin or insulin glargine. In an unpublished study, insulin detemir was effective in improving control of glycemia in thirteen diabetic

TABLE 6-7 **COMPARISON OF INSULIN PREPARATION DOSAGES REQUIRED TO ATTAIN CONTROL OF GLYCEMIA IN DIABETIC DOGS**

		Insulin Dosage (U/kg/injection)		
INSULIN PREPARATION	**NUMBER OF DOGS**	**MEDIAN**	**RANGE**	**STUDY**
NPH	54	0.8* 0.4†	0.4-1.9 0.3-0.8	Lorenzen, 1992
Lente	35	0.8	0.3-1.4	Monroe et al, 2005
PZI	17	0.9	0.4-1.5	Della-Maggiore et al, 2012
Glargine	12	0.6	0.1-1.1	Fracassi et al, 2012
Detemir	13	0.2	NR	Ford, 2010
Detemir	15	0.3	0.1-0.6	UCD, 2013‡

NPH, Neutral protamine Hagedorn; *NR,* not reported; *PZI,* protamine zinc insulin.
*Dogs weighing < 15 kg
†Dogs weighing ≥ 15 kg
‡UCD, 2013: Insulin dosage required to attain glycemic control in 15 of 24 diabetic dogs treated with insulin detemir at UC Davis veterinary hospital; glycemic control could not be attained using detemir in 9 of the 24 dogs.

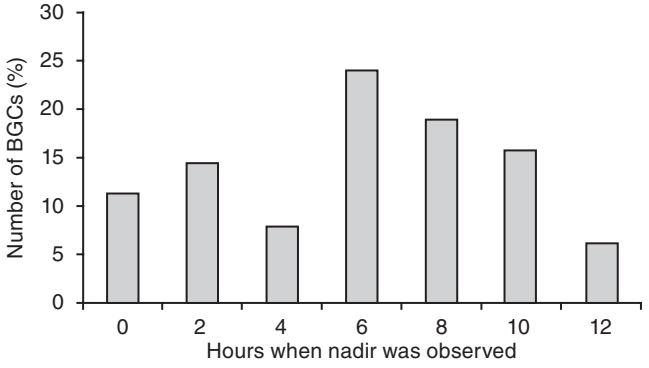

FIGURE 6-9 Histograms indicate the number of blood glucose curves (BGCs; %) from 12 dogs with diabetes mellitus treated by the administration of various doses of insulin glargine twice daily for 24 weeks where the glucose nadir was observed before (0) or 2, 4, 6, 8, 10, or 12 hours after insulin injection, respectively. (From Fracassi F, et al.: Use of insulin glargine in dogs with diabetes mellitus, *Vet Rec* 170:52, 2012.)

dogs managed with home blood glucose monitoring during a 4 to 24 month (median, 10 month) period (Ford et al, 2010). Ten of 13 dogs were previously treated with NPH or Lente insulin with poor results. The mean and median insulin dosage on the last week of evaluation was 0.45 and 0.22 U/kg/injection. Biochemical hypoglycemia (blood glucose less than 60 mg/dL; 3.4 mmol/L) was identified in approximately 2% of all blood glucose measurements and occurred on average 7.5 times per dog during the study. Our experiences with insulin detemir in dogs have been mixed but better than our experiences with insulin glargine. The absorption of insulin detemir from the subcutaneous site of injection is variable. In some diabetic dogs, the absorption is slow and sustained, resulting in relatively flat blood glucose curves (Fig. 6-11). In other dogs, the absorption is similar to that seen with intermediate-acting insulin preparations like Lente, resulting in U-shaped blood glucose curves (see Fig. 6-24). The most common problem with insulin detemir has been hypoglycemia and induction of glucose counterregulation (i.e., Somogyi response) when insulin detemir is given twice a day (see Insulin Overdosing and Glucose Counterregulation [Somogyi Response]). We do not consider insulin detemir a first choice insulin for the treatment of

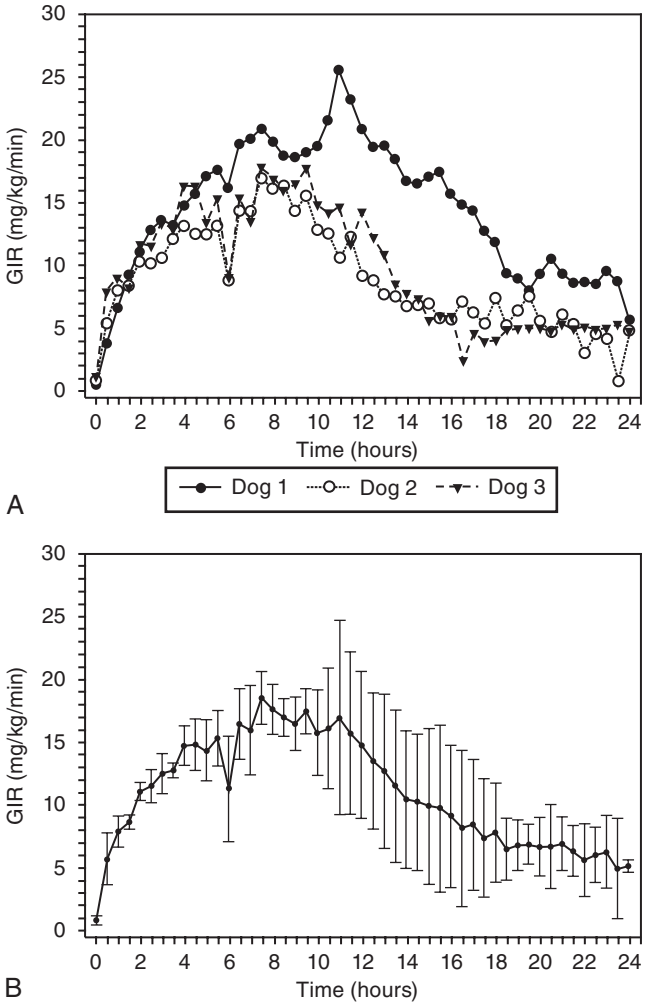

FIGURE 6-10 Time-action profile of insulin detemir over a 24-hour period in three individual healthy non-diabetic dogs **(A)** and mean ± standard deviation (SD) results in the three dogs **(B).** Results are presented as glucose infusion rate *(GIR)* required to maintain euglycemia after the subcutaneous (SC) administration of 0.5 U/kg insulin detemir at time 0. Higher values of GIR indicate stronger insulin action. (From Sako T, et al.: Time-action profiles of insulin detemir in normal and diabetic dogs, *Res Vet Sci* 90:396, 2011.)

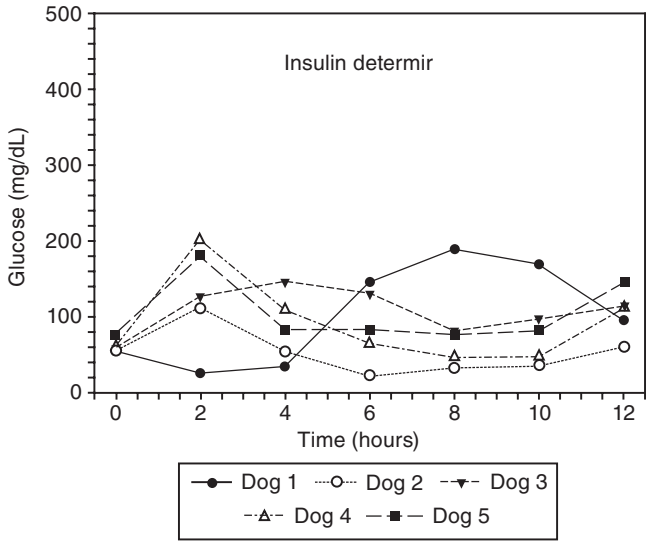

FIGURE 6-11 Results of 12-hour serum glucose curves after subcutaneous (SC) administration of various doses of insulin detemir twice a day for 5 days in five insulin-dependent diabetic dogs. Insulin detemir dosages administered at time 0 on day 5 were as follows: *Dog 1,* 0.23 U/kg; *Dog 2,* 0.19 U/kg; *Dog 3,* 0.09 U/kg; *Dog 4,* 0.18 U/kg; and *Dog 5,* 0.07 U/kg. (From Sako T, et al.: Time-action profiles of insulin detemir in normal and diabetic dogs, *Res Vet Sci* 90:396, 2011.)

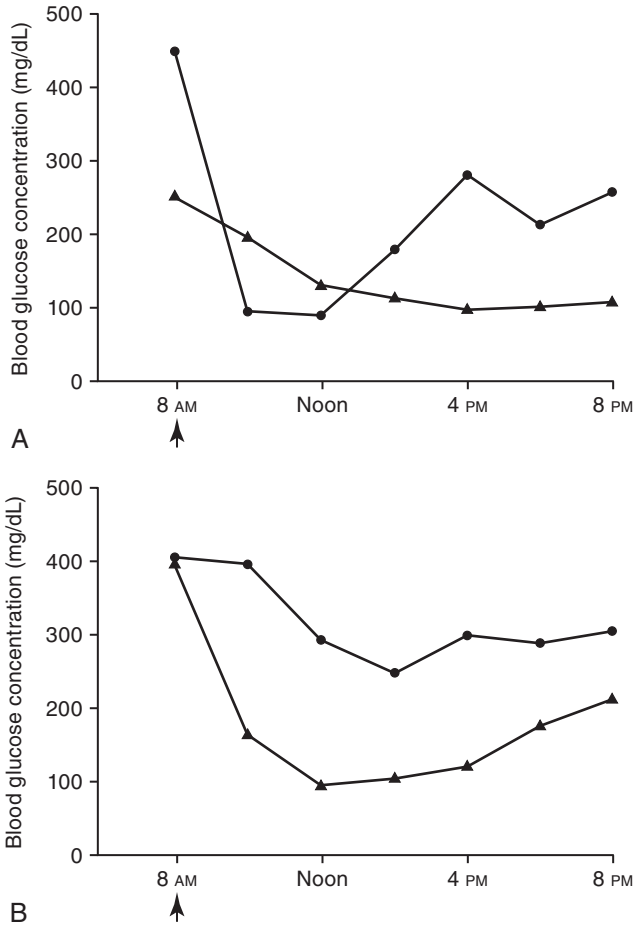

FIGURE 6-12 **A,** Blood glucose curve in a miniature poodle receiving recombinant human Lente insulin, 6 U/kg body weight *(solid line, triangles)* and recombinant human 70/30 neutral protamine Hagedorn (NPH)/regular insulin, 3 U/kg body weight *(solid line, circles)* subcutaneous (SC). **B,** Blood glucose curve in an 8 kg cat receiving 4 U recombinant human Ultralente insulin *(solid line, circles)* and 4 U of recombinant human 70/30 NPH/regular insulin *(broken line, triangles)* SC. (From Nelson RW: Diabetes mellitus. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 4, Philadelphia, 1995, Saunders, p. 1528.) ↑ = insulin injection and food.

diabetes in dogs but consider it the insulin of choice in diabetic dogs with problems of short duration of effect of NPH and Lente insulin. Our starting dosage for insulin detemir is 0.1 U/kg twice a day.

Insulin Mixtures. Mixtures of short- and long-acting insulin have been developed in an attempt to mimic the increase in portal insulin concentrations during and immediately following consumption of a meal, thereby minimizing postprandial hyperglycemia. NPH insulin can be mixed with regular crystalline insulin, and if injected immediately, the regular insulin remains rapid-acting. Stable premixed 75% NPH/25% regular, 70% NPH/30% regular, and 50% NPH/50% regular preparations are available (e.g., Humulin 70/30 and Mixtard 70/30). Similarly, mixtures of lispro and lispro protamine suspension (e.g., Humalog Mix 75/25 and Humalog Mix 50/50) and aspart and aspart protamine suspension (e.g., Novolog Mix 70/30) are available. In our experience, these premixed preparations are quite potent, causing a rapid decrease in blood glucose concentration within 60 to 90 minutes of subcutaneous administration (Fig. 6-12). In addition, the duration of effect has usually been short (less than 8 hours). We generally use these insulin mixtures only as a last resort when more conventional insulin preparations have been ineffective in establishing control of glycemia. Although regular insulin remains fast acting when added to NPH, when added to Lente insulin, regular insulin binds to excess zinc in the vial of Lente, blunting regular insulin's quick effect (Galloway, 1988).

Insulin Storage, Mixing, and Dilution

Freezing and heating the insulin bottle will inactivate insulin in the bottle. Historically, shaking the bottle of NPH, Lente, or PZI insulin was believed to inactivate the insulin, but recent studies performed by the pharmaceutical company have shown that shaking the bottle of Lente insulin does not impact insulin action, provides more uniform dispersal of insulin throughout the solution than rolling the bottle, and is currently recommended. Similar recommendations have not yet been reported for NPH and PZI insulins. Although keeping the bottle of insulin at "room temperature" does not inactivate insulin, we routinely instruct clients to store the insulin bottle in the door of the refrigerator to maintain a consistent environment. Some veterinarians advocate replacing insulin with a new bottle every 1 to 2 months to prevent problems caused by loss of activity or sterility. This practice can create financial hardship for some clients and may not be necessary. The shelf life of a bottle of insulin that has been stored appropriately is longer than manufacturer recommendations. We have not appreciated a clinically significant loss of insulin action with time when insulin preparations, including glargine and detemir, are maintained in a constant environment (i.e., refrigerator) and handled appropriately. Routinely purchasing a new bottle of insulin every month may not be necessary, especially if the diabetic dog is doing well. However, development of cloudiness or discoloration suggest contamination, change in pH of the solution (glargine), and/or loss of insulin activity. The bottle of insulin should be discarded and replaced with a new bottle of insulin. Similarly, loss of insulin activity in the bottle should always be considered whenever clinical signs recur, regardless of the quantity of insulin remaining in the bottle.

Dilution of insulin is a common practice, especially in very small dogs and cats. Only diluting solutions provided by the respective company should be used. Although studies evaluating the shelf-life of diluted insulin have not been published, I recommend replacing diluted insulin preparations every 4 to 8 weeks. Even when these guidelines are observed, insufficient amounts of insulin are administered when diluted insulin is used in some dogs and cats, despite appropriate dilution and insulin administration techniques. These inadequacies are corrected when full-strength insulin is used. It is important to remember that insulin glargine is pH dependent and should not be diluted with solutions that may change the pH of the solution.

See Chapter 7 for additional information on insulin preparations, insulin handling, and owner instructions.

Initial Insulin Treatment Recommendations

Once the diagnosis of diabetes is established, dogs should be considered insulin dependent and treatment with insulin should be initiated. Porcine source Lente insulin (Vetsulin, Caninsulin) is the initial insulin of choice for treating newly-diagnosed diabetic dogs (see Table 6-6). Recombinant human NPH insulin is also effective but problems with short duration of effect are common with NPH insulin. Studies to date suggest that the median dosage of Lente and NPH insulin required to attain glucose control in most diabetic dogs is approximately 0.5 U/kg/injection, with a range of 0.2 to 1.0 U/kg (see Table 6-7). One important goal in the initial regulation of the diabetic dog is avoidance of symptomatic hypoglycemia, especially in the home environment. For this reason, the starting insulin dosage should be on the low end of the range (i.e., approximately 0.25 U/kg). Dietary therapy is initiated concurrently (see later). We routinely start with twice a day insulin administration because the overwhelming majority of diabetic dogs require Lente and NPH insulin twice a day (Hess and Ward, 2000; Monroe et al, 2005). Establishing control of glycemia is easier and problems with hypoglycemia and the Somogyi response (see Insulin Overdosing and Glucose Counterregulation [Somogyi Response]) are less likely when twice daily insulin therapy is initiated while the insulin dose is low (i.e., at the time insulin treatment is initiated).

Although recombinant human PZI, insulin glargine, and insulin detemir are effective in controlling glycemia in some diabetic dogs, problems with consistency of effect, variable and unpredictable timing of the glucose nadir, prolonged duration of effect, and suspected induction of the Somogyi response preclude recommending these insulin preparations in the newly-diagnosed diabetic dog. However, these insulin preparations should be considered when problems caused by short duration of insulin effect develop with Lente or NPH insulin (see Complications of Insulin Therapy).

Initial Adjustments in Insulin Therapy

Diabetic dogs require several days to equilibrate to changes in insulin dosage or preparation. Newly-diagnosed diabetic dogs are typically hospitalized for no more than 24 to 48 hours to finish the diagnostic evaluation and begin insulin therapy. During hospitalization, blood glucose concentrations are typically determined at the time insulin is administered and at 3, 6, and 9 hours later. The intent is to identify hypoglycemia (blood glucose less than 80 mg/dL; 4.5 mmol/L) in those dogs that are unusually sensitive to the actions of insulin. If hypoglycemia occurs, the insulin dosage is decreased prior to sending the dog home. A minor adjustment in the insulin dosage may be done in those dogs that remain hyperglycemic during these first few days of insulin therapy; however, the objective during this first visit is *not* to establish perfect glycemic control before sending the dog home. Rather, the objective is to begin to reverse the metabolic derangements induced by the disease, allow the dog to equilibrate to the insulin and change in diet, teach the owner how to administer insulin, and give the owner a few days to become accustomed to treating the diabetic dog at home. Adjustments in insulin therapy are made on subsequent evaluations once the owner and pet have gotten used to the treatment regimen.

Diabetic dogs are typically evaluated once weekly until an effective insulin treatment protocol is identified. Glycemic control is attained when clinical signs of diabetes have resolved; the pet is healthy and interactive in the home; its body weight is stable (unless the dog is undergoing weight loss to correct obesity); the client is satisfied with the progress of therapy; and, if possible, the blood glucose concentrations range between 100 and 250 mg/dL (5.6 to 14 mmol/L) throughout the day. The client is informed at the time insulin therapy is initiated that it will take approximately 1 month to establish a satisfactory insulin treatment protocol, assuming unidentified insulin-antagonistic disease is not present. The goals of therapy are also explained to the client. During this month, changes in insulin dose and possibly insulin type are common and should be anticipated by the client. At each evaluation the client's subjective opinion of water intake, urine output, and overall health of the pet is discussed; a complete physical examination is performed; change in body weight noted; and serial blood glucose measurements obtained over a 10- to 12-hour period after insulin administration are assessed. Adjustments in insulin therapy are based on this information, the pet is sent home, and an appointment is scheduled for the next week to reevaluate the response to any change in therapy. If the dog remains poorly controlled, the dose of insulin is gradually increased by 1 to 5 U/injection (depending on the size of the dog) each week until control is attained. This gradual increase in dose helps prevent hypoglycemia and the Somogyi response. Control of glycemia can be established in most dogs using insulin doses in the range of 1.0 U of insulin/kg or less (median, 0.5 U/kg) administered twice each day. If the insulin dose exceeds 1.0 U/kg/injection without adequate glycemic control, then further investigations to determine the reason for treatment failure are indicated (see Complications of Insulin Therapy). If hypoglycemia is noted either clinically or biochemically at any time, the insulin dosage should be decreased and further adjustments in the insulin dose performed as needed to attain glycemic control.

Many factors affect the dog's glycemic control from day to day, including variations in insulin administration and absorption, dietary indiscretions and caloric intake, amount of exercise, and variables that affect insulin responsiveness (e.g., stress, concurrent inflammation, infection). As a consequence, the insulin dosage required to maintain glycemic control typically changes (increase or decrease) with time. Initially, a fixed dosage of insulin is administered at home during the first few months of therapy, and changes in insulin dosage are made only after the owner consults with the veterinarian. As the insulin dose range required to maintain glycemic control becomes apparent and as confidence is gained in the client's ability to recognize signs of hypoglycemia and hyperglycemia, the client is eventually allowed to make *slight* adjustments in the insulin dose at home on the basis of clinical observations of the pet's well-being. However, the client is instructed to stay within the agreed-upon insulin dose range. If the insulin dose is at the upper or lower end of the established range and the pet is still symptomatic, the client is instructed to call the veterinarian before making further adjustments in the insulin dose.

Dietary Therapy

Diet plays an important role in the management of the diabetic dog (Box 6-3). What diet is ultimately fed is dictated, in part, by the weight of the dog, concurrent disease, and owner and dog preferences. Correction of obesity is the most beneficial step that can be taken to improve control of glycemia. Obesity-induced insulin resistance has been documented in dogs and is an important factor accounting for variations in response to insulin therapy in diabetic dogs (Gayet et al, 2004; Yamka et al, 2006). Weight loss improves insulin resistance in obese diabetic dogs. Weight loss usually requires a combination of restricting caloric intake, feeding low calorie-dense diets, and increasing caloric expenditure through exercise. Diets specifically designed for weight loss should be considered for obese diabetic dogs to promote weight loss. Weight loss diets contain higher quantities of insoluble fiber than diabetic diets and lower fat content to decrease the caloric density of the food. High-fiber, low calorie-dense diets should not be fed to thin or emaciated diabetic dogs until control of glycemia is established and a normal body weight is attained using a higher-calorie-dense, lower-fiber diet designed for maintenance.

Most premium pet food companies offer diets designed for diabetic dogs (see Box 6-3). The composition of these diets varies but most contain fiber. Increasing the fiber content of the diet is beneficial for treating obesity and improving control of glycemia in diabetic dogs (Nelson et al, 1991; 1998; Graham et al, 1994; Fig. 6-13). The ability of the food fiber to form a viscous gel and thus impair convective transfer of glucose and water to the absorptive surface of the intestine appears to be of greatest importance in slowing intestinal glucose absorption. The more rapidly fermentable viscous soluble fibers (e.g., gums, citrus pectin) slow glucose diffusion to a greater degree than the slowly fermentable less viscous insoluble fibers (e.g., cellulose, hemicellulose) and, as such, are believed to be of greater benefit in improving control of glycemia. Most diabetic diets contain a blend of soluble and insoluble fiber sources, including moderately fermentable fibers (e.g., rice bran, soy fiber, beet pulp) that have both soluble and insoluble fiber characteristics.

Complications of feeding diabetic diets containing high fiber content include excessive frequency of defecation, constipation, obstipation, soft stools, excessive flatulence, and refusal to eat the diet (Box 6-4). Most of these problems will resolve by changing the type or quantity of fiber consumed (i.e., a change in the diet). Problems with palatability are usually a result of too rapid of a switch from the dog's usual diet to the diabetic diet or a result of boredom after consuming the diabetic diet for months. If palatability is a problem initially, the dog can be gradually switched from its regular diet to a diabetic diet over a 2- to 4-week period. Periodic changes in the types of diabetic diets and mixtures of diabetic diets have been helpful in alleviating the problem of boredom with a diet. Palatability issues affiliated with feeding diets containing an increased amount of fiber should always be considered in the list of differential diagnoses for inappetence in a diabetic dog.

Type and quantity of carbohydrate in the diet may also affect post-prandial blood glucose concentrations. For example, sorghum and barley have a lower glycemic index (i.e., lower impact on postprandial blood glucose and insulin concentrations) than rice. Some diabetic diets for dogs use low glycemic index carbohydrates in an effort to minimize post-prandial hyperglycemia. Digestible carbohydrate content of the diet (i.e., percentage of metabolizable energy derived from carbohydrates) also affects post-prandial blood glucose concentrations (Nguyen et al, 1998). In a recent study, consumption of a lower carbohydrate-containing diet resulted in lower post-prandial blood glucose concentrations in healthy dogs, compared with a maintenance diet and a diabetic diet containing increased carbohydrate content (Elliott et al, 2012). Although diets with moderate versus high carbohydrate content may be preferred for diabetic dogs, a corresponding increase in the percent metabolizable energy derived from fat should be minimized to avoid an increase in blood lipid parameters, including cholesterol, triglycerides, free glycerol, and free fatty acids (Fleeman et al, 2009b). Derangements in fat metabolism are common in diabetic dogs and include increased serum concentrations of cholesterol, triglycerides, lipoproteins, chylomicrons, and free fatty acids, hepatic lipidosis, atherosclerosis, and a predisposition for development of pancreatitis (Hess et al, 2002). Dietary fat may also cause insulin resistance, promote hepatic glucose production, and in healthy dogs, suppress beta-cell function (Massillon et al, 1997; Kaiyala et al, 1999). Low fat highly digestible diets (e.g., Royal Canin Gastrointestinal Low Fat Diet) are an alternative to fiber-containing diabetic diets, especially if acute or chronic pancreatitis or persistent hyperlipidemia are concurrent problems or palatability is a problem with diabetic diets. A higher fat content may be needed for weight gain in thin or emaciated diabetic dogs. Feeding lower-fat diets may help minimize the risk of pancreatitis, control some aspects of hyperlipidemia, and reduce overall caloric intake to favor weight loss or maintenance (Remillard, 1999).

BOX 6-3 Recommendations for Dietary Treatment of Diabetes Mellitus in Dogs

Correct obesity and maintain body weight in an acceptable range.
Control daily caloric intake.
Increase daily exercise.
Avoid excessive amounts of insulin.
Maintain consistency in the timing and caloric content of the meals.
Feed within the time frame of insulin action.
Feed one half the daily caloric intake at the time of each insulin injection with every 12-hour insulin therapy or at the time of the insulin injection and 6 to 10 hours later with every 24-hour insulin therapy.
Minimize the impact of food on postprandial blood glucose concentrations.
Avoid monosaccharides and disaccharides, propylene glycol, and corn syrup.
Let "nibbler" dogs nibble throughout the day and night; ensure that other pets do not have access to the food; provide one-half of total daily calories at time of each insulin injection.
Increase the fiber content of the diet.

Examples of Veterinary Diets Designed for Diabetic Dogs
Hill's Prescription Diet w/d
Hill's Prescription Diet r/d (obese diabetic dog)
Purina DCO
Purina OM (obese diabetic dog)
Royal Canin Diabetic

Feeding Schedule

The feeding schedule should be designed to enhance the actions of insulin and minimize postprandial hyperglycemia. The development of postprandial hyperglycemia depends, in part, on the amount of food consumed per meal, the rate at which glucose and other nutrients are absorbed from the intestine, and the effectiveness of exogenous insulin during the postprandial period. The daily caloric intake should be ingested when insulin is still present

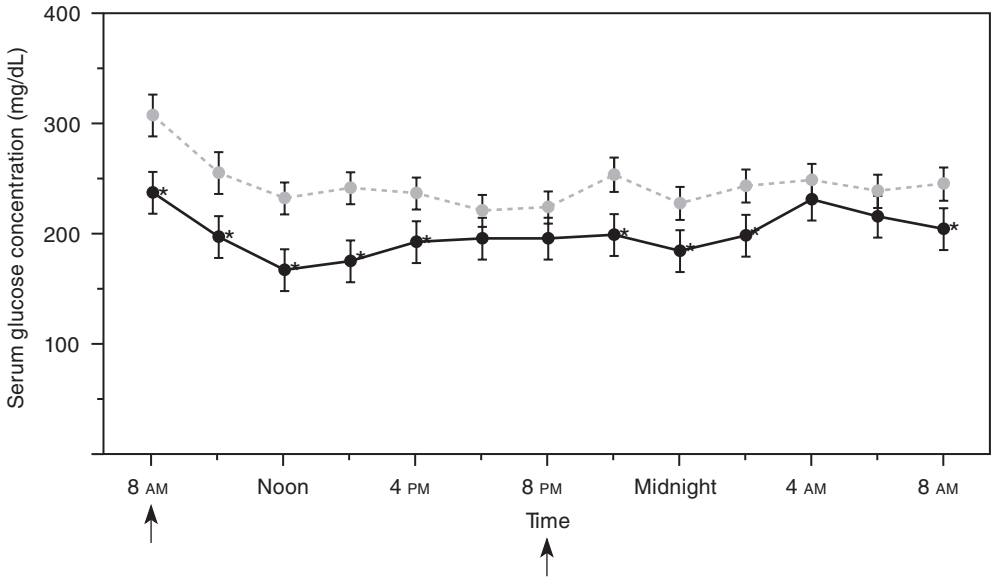

FIGURE 6-13 Mean (± standard error of the mean) serum concentrations of glucose in eleven dogs with naturally occurring diabetes mellitus fed high-insoluble fiber (i.e., cellulose; *solid line*) and low-fiber *(broken line)* diet. (From Nelson RW, et al.: Effect of dietary insoluble fiber on glycemic control in dogs with naturally-occurring diabetes mellitus, *J Am Vet Med Assoc* 212:380, 1998.) ↑ = Insulin administration and consumption of half of daily caloric intake; * = $p < 0.05$, compared with low fiber diet.

BOX 6-4 Common Complications Associated with Feeding Diets Containing Increased Quantities of Fiber

Inappetence caused by poor palatability or boredom with food
Increased frequency of defecation
Constipation and obstipation (insoluble fiber)
Soft stools and diarrhea (soluble fiber)
Increased flatulence (soluble fiber)
Weight loss
Hypoglycemia

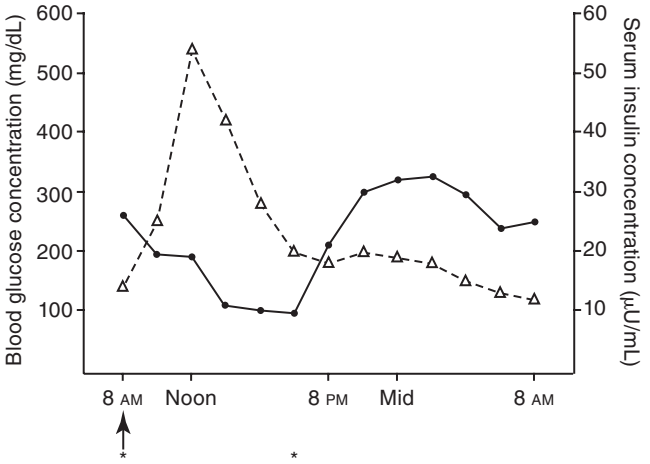

FIGURE 6-14 Mean blood glucose *(solid line)* and serum insulin *(broken line)* concentrations in eight dogs with diabetes mellitus treated with beef/pork source neutral protamine Hagedorn (NPH) insulin subcutaneously once daily. The duration of NPH effect is too short, resulting in prolonged periods of hyperglycemia beginning shortly after feeding the evening meal. (From Nelson RW: Diabetes mellitus. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 4, Philadelphia, 1995, Saunders, p. 1525.) ↑ = Insulin injection; * = equal-sized meals consumed.

in the circulation and is capable of disposing of glucose absorbed from the meal. If the meals are consumed while exogenous insulin is still metabolically active, the postprandial increase in blood glucose concentration is minimal or absent. In contrast, feeding the diabetic dog after insulin action has waned results in increasing blood glucose concentration beginning 1 to 2 hours postprandially (Fig. 6-14). If this occurs, either the type of insulin, frequency of insulin administration, or timing of the meals in relationship to the insulin injection should be adjusted.

Typically, dogs receiving exogenous insulin twice a day are fed equal-sized meals at the time of each insulin injection. If the dog is receiving exogenous insulin once a day, one half of the daily caloric intake is fed at the time of the insulin injection and the remaining half approximately 8 hours later. Unfortunately, the eating behavior of dogs varies considerably, from finicky eaters that nibble on food periodically throughout the day to gluttonous dogs that quickly consume everything placed in their food dish. Gluttonous dogs are fed as discussed earlier. Finicky dogs generally resist attempts by owners to convert them to a "gluttonous" type of eating behavior, which can be frustrating to the owner instructed to have their pet eat all of its food at the time of the insulin injection. However, if one adheres to the principle that feeding multiple small meals rather than one large meal within the time frame of insulin action helps minimize the hyperglycemic effect of each meal, then allowing a finicky eater to eat whenever it wants should help control fluctuations in blood glucose. For this reason, dogs that are finicky and nibble throughout the day should be allowed to continue their pattern of eating. For these dogs, half of the total daily food intake should be available beginning at the time of each insulin injection and the dog allowed to choose when and how much to eat. The dog should have access to the food throughout the day and night, and other dogs in the household cannot have access to the food.

Modifications in Dietary Therapy

Concurrent disease in which diet is an important aspect of therapy also dictates the type of diet to be fed. For example, diabetic dogs with concurrent chronic pancreatitis or exocrine pancreatic insufficiency (pancreatic acinar atrophy) should be fed a low fat, low fiber, highly digestible diet. Diabetic dogs with CKD should be fed a lower protein diet designed for kidney failure. Diabetic dogs with concurrent inflammatory bowel disease may need a

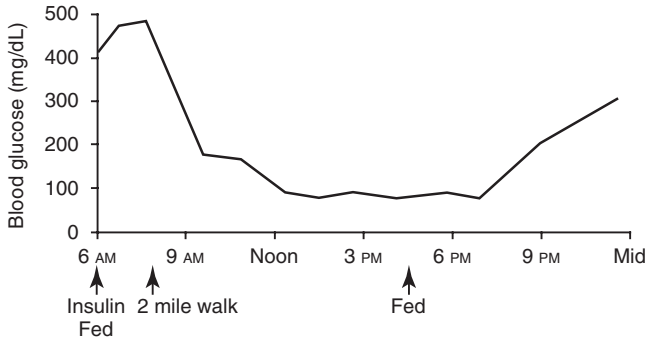

FIGURE 6-15 Serial blood glucose curve obtained by the owner at home after the administration of 1 U/kg porcine Lente insulin to a 35 kg male-castrate diabetic Labrador Retriever. The treatment regimen adopted by the owner included the administration of porcine Lente insulin once a day at 6 AM, equal-sized meals fed at 6 AM and 5 PM, and a 2-mile walk beginning at 9 AM. The owner was obtaining blood glucose curves almost every day and adjusting the insulin dose based on the results. The blood glucose concentration typically decreased 70 to 140 mg/dL after the walk as illustrated in this glucose curve, compared with days when the dog was not walked. The owner sought help because of persistence of polyuria and polydipsia, especially at night, despite increasing the insulin dose. Polyuria and polydipsia improved with initiation of twice a day administration of porcine Lente insulin and feeding the dog at the time of each insulin injection.

hypoallergenic diet to help control inflammation and clinical signs. Whenever possible, dietary therapy for all disorders should be "blended"; however, if this is not possible, dietary therapy for the most serious disorder should take priority. For example, dietary therapy for chronic renal failure, heart failure, or recurring pancreatitis is a higher priority than dietary therapy for diabetes mellitus. Dietary therapy for diabetes mellitus should be considered adjunctive; glycemic control can be maintained with insulin, regardless of the diet fed.

Exercise

Exercise plays an important role in maintaining glycemic control in the diabetic dog by helping promote weight loss and by eliminating the insulin resistance induced by obesity. Exercise also has a glucose-lowering effect by increasing the mobilization of insulin from its injection site, presumably resulting from increased blood and lymph flow, by increasing blood flow (and therefore insulin delivery) to exercising muscles, by stimulating translocation (i.e., upregulation) of glucose transporters (primarily GLUT-4) in muscle cells, and by increasing glucose effectiveness (i.e., ability of hyperglycemia to promote glucose disposal at basal insulin concentrations) (Fernqvist et al, 1986; Galante et al, 1995; Phillips et al, 1996; Nishida et al, 2001; Fig. 6-15). The daily routine for diabetic dogs should include exercise, preferably at the same time each day and not around the time of peak insulin effect. Strenuous and sporadic exercise can cause severe hypoglycemia and should be avoided. If unavoidable, the insulin dose should be decreased in dogs subjected to sporadic strenuous exercise on those days of anticipated increased exercise. The reduction in insulin dose required to prevent hypoglycemia is variable and determined by trial and error. Reducing the insulin dose by 50% initially is recommended, and further adjustments should be based on measurement of blood glucose concentration with a portable blood glucose monitor during exercise, the occurrence of symptomatic hypoglycemia, and the severity of polyuria and polydipsia that develops during the ensuing 24 to 48 hours. In addition, owners must be aware of the signs of hypoglycemia and have a source of glucose (e.g., candy, food, sugar solution) readily available to give their dog should any of these signs develop.

Oral Hypoglycemic Drugs

Oral hypoglycemic drugs work by stimulating pancreatic insulin secretion (e.g., sulfonylureas, meglitinides, glucagon-like peptide-1 [GLP-1] receptor agonists, dipeptidyl peptidase-4 [DPP-4] inhibitors), inhibiting glucagon secretion (e.g., DPP-4 inhibitors or gliptins), enhancing tissue sensitivity to insulin (e.g., metformin, thiazolidinediones), or slowing postprandial intestinal glucose absorption (α-glucosidase inhibitors). Although controversial, chromium and vanadium are trace minerals that may also function as insulin sensitizers. Oral hypoglycemic drugs are primarily used for the treatment of type 2 diabetes; a form of diabetes that is not recognized in dogs. Oral sulfonylurea drugs (e.g., glipizide, glyburide) directly stimulate insulin secretion by beta cells and are the most commonly used oral hypoglycemic drugs for the treatment of diabetes mellitus in humans and cats but are ineffective in diabetic dogs, presumably because dogs have an inadequate mass of functional beta cells at the time diabetes is diagnosed.

Acarbose

Acarbose is a complex oligosaccharide of microbial origin that competitively inhibits pancreatic alpha-amylase and alpha-glucosidases (glucoamylase, sucrase, maltase, and isomaltase) in the brush border of the small intestinal mucosa, which delays digestion of complex carbohydrates, delays absorption of glucose from the intestinal tract, and decreases postprandial blood glucose concentrations. Placebo-controlled clinical studies completed in healthy and diabetic dogs documented a decrease in postprandial total glucose absorption and total insulin secretion when healthy dogs were treated with acarbose (compared with placebo) and a decrease in daily insulin dose, mean blood glucose concentration during an 8 hour blood sampling period, and blood glycated protein concentrations in diabetic dogs treated with acarbose (compared with placebo) (Robertson et al, 1999; Nelson et al, 2000; Fig. 6-16). Although acarbose may be beneficial in improving control of glycemia in some dogs with insulin-requiring diabetes, the high prevalence of adverse effects (diarrhea and weight loss) resulting from carbohydrate malassimilation and the expense of the drug limit its usefulness.

Chromium

Chromium is a ubiquitous trace element that exerts insulin-like effects in vitro. The exact mechanism of action is not known, but the overall effect of chromium is to increase insulin sensitivity, presumably through a post-receptor mechanism of action (Anderson, 1992; Striffler et al, 1995; Anderson et al, 1997). Chromium does not increase serum insulin concentrations. Chromium is an essential cofactor for insulin function, and chromium deficiency results in insulin resistance. In one study, dietary chromium picolinate supplementation improved results of an intravenous (IV) glucose tolerance test in healthy dogs, compared with healthy dogs not treated with chromium (Spears et al, 1998). Other studies failed to identify an effect of dietary chromium picolinate supplementation on glucose tolerance in obese dogs during weight reduction (Gross et al, 2000) nor did it improve control of glycemia in the diabetic dogs treated with 200 to 400 μg of chromium picolinate by mouth twice daily (Schachter et al, 2001; Fig. 6-17). Chromium picolinate is considered a nutraceutical in the United States and can be purchased in health food and drug stores. It is inexpensive, and there are no known toxic effects associated with its ingestion.

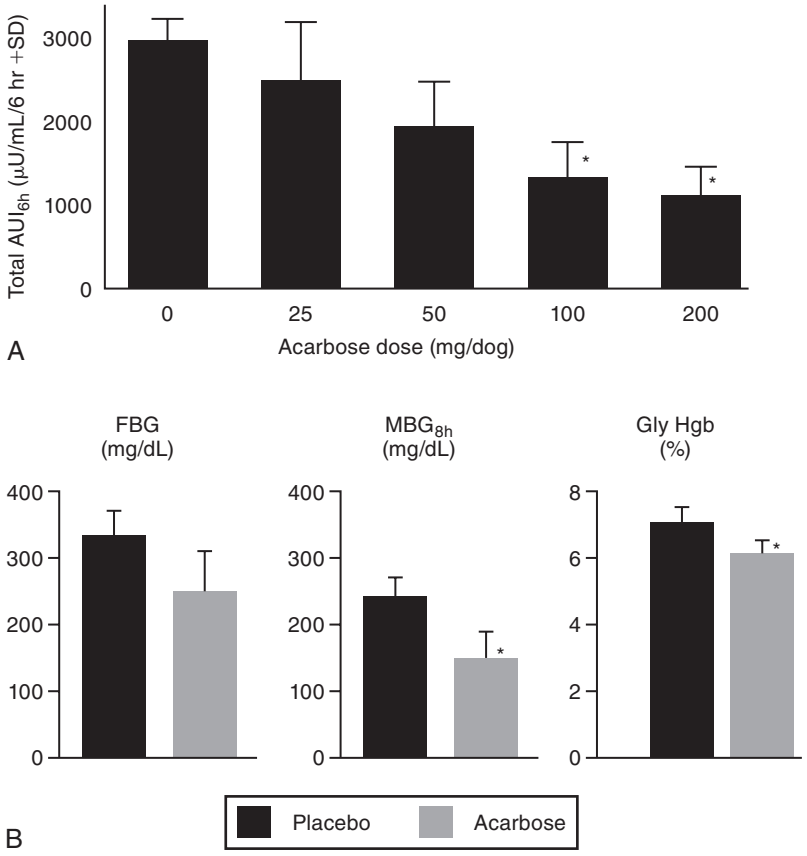

FIGURE 6-16 **A,** Mean total insulin secretion for five healthy dogs during the first 6 hours after consumption of a meal and a placebo or 25, 50, 100, or 200 mg of acarbose. *T-bars* represent standard error of the mean. **B,** Fasting blood glucose *(FBG),* mean blood glucose over an 8-hour time period *(MGB_{8h}),* and blood total glycosylated hemoglobin *(Gly Hgb)* in five dogs with insulin-dependent diabetes mellitus treated with insulin and placebo *(black bars)* and insulin and acarbose *(gray bars)* for 2 months each in a randomly assigned treatment sequence. *T-bars* represent standard deviation. (**A,** From Robertson J, et al.: Effects of the alpha-glucosidase inhibitor acarbose on postprandial serum glucose and insulin concentrations in healthy dogs, *Am J Vet Res* 60:541, 1999.) **A**, **B**, * = $p < 0.05$, compared with value obtained after treatment with placebo.

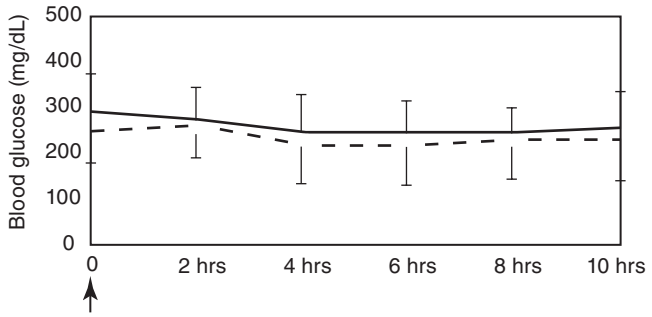

FIGURE 6-17 Mean (± standard deviation) blood glucose concentrations obtained from 13 dogs with insulin-dependent diabetes mellitus before insulin and feeding (8 AM = Time 0) and for 10 hours after insulin administration only *(broken line)* or after insulin and chromium tripicolinate administration *(solid line).* Dogs were treated for 3 months with insulin and then 3 months with insulin and chromium tripicolinate. Mean blood glucose concentrations are the mean of all corresponding blood glucose values obtained during the 10-hour blood sample collection period for each dog at 1, 2, and 3 months of each treatment period. (From Schachter S, et al.: Oral chromium picolinate and control of glycemia in insulin-treated diabetic dogs, *J Vet Intern Med* 15:379, 2001.) ↑ = time of insulin or insulin and chromium picolinate administration.

Herbs, Supplements, and Vitamins

Alternative therapies that include herbs, supplements, and vitamins in conjunction with or in lieu of the more conventional treatment options have been used by some individuals with type 2 diabetes. The goals for using herbs, supplements, and vitamins are primarily centered around decreasing blood glucose, triglyceride, and cholesterol concentrations; delaying the onset of long-term complications of diabetes (e.g., coronary artery disease, retinopathy); and improving the overall well-being of the patient (Roszler, 2001; Box 6-5). Proposed beneficial effects vary with the herb, supplement, or vitamin utilized and include delaying nutrient absorption from the gastrointestinal tract, stimulating insulin secretion, improving insulin sensitivity, altering lipid metabolism, improving circulation, and benefits attributed to antioxidant properties. Some herbs, supplements, and vitamins (e.g., ginseng, chromium, fish oils, and psyllium) have been critically evaluated for efficacy, whereas others are recommended based primarily on folklore and testimonials (Pastors et al, 1991; Striffler et al, 1995; Vuksan et al, 2001). Critical studies assessing the effects of herbs, supplements, and vitamins on diabetic control and complications are needed before these alternative therapies can be recommended in diabetic dogs. Intuitively, it seems doubtful that the herbs, supplements, and vitamins listed in Box 6-5 will have much of an impact in diabetic dogs—in part because these therapies are primarily used for treating type 2 diabetes, which is not recognized in diabetic dogs, and delaying chronic diabetic complications, which are uncommon in dogs.

Identification and Control of Concurrent Problems

Concurrent disease and administration of insulin-antagonistic drugs are commonly identified in the dog with newly-diagnosed diabetes mellitus (Hess et al, 2000b; Peikes et al, 2001). Concurrent disease and insulin-antagonistic drugs can interfere with tissue responsiveness to insulin, resulting in insulin resistance and poor control of the diabetes. Concurrent disease and insulin-antagonistic drugs typically cause insulin resistance by altering insulin metabolism (prereceptor problem), by decreasing the

BOX 6-5 Herbs, Supplements, and Vitamins that have been Used to Treat Diabetes Mellitus in Humans

Improve Hyperglycemia
Alpha-lipoic acid
Vitamin C
Vitamin E
Chromium
Vanadium
Fenugreek seeds
American and Asian ginseng
Gymnema sylvestre
Psyllium seeds
Cinnamon

Prevent Coronary Artery Disease
Vitamin C
Vitamin E
Quercetin

Improve Circulation
Gingko biloba
Pycnogenol

Prevent/Control Pain from Neuropathy
Alpha-lipoic acid
Vitamin B6
Capsaicin (cayenne pepper) (topical ointment)
Evening primrose oil

Improve Hyperlipidemia
Vitamin E
Evening primrose oil
Fish oils (e.g., omega-3 fatty acids)
Selenium

Prevent Cataracts
Alpha-lipoic acid
Vitamin C

Prevent Retinopathy
Vitamin E
Pycnogenol (pine bark extract)

Antioxidant
Alpha-lipoic acid
Vitamin A
Vitamin C
Vitamin E
Pycnogenol
Quercetin
Selenium

From Roszler J: Herbs, supplements and vitamins: what to try, what to buy, *Diabetes Interviews* August: 45, 2001.

concentration or binding affinity of insulin receptors on the cell membrane (receptor problem), by interfering with the insulin receptor signaling cascade (postreceptor problem), or by a combination of these. Depending on the etiology, insulin resistance may be mild and easily overcome by increasing the dose of insulin (e.g., obesity); may be severe, causing sustained and marked hyperglycemia regardless of the type and dose of insulin administered (e.g., hyperadrenocorticism); or may fluctuate in severity over time (e.g., chronic pancreatitis). Some causes of insulin resistance are readily apparent at the time diabetes is diagnosed, such as obesity and the administration of insulin-antagonistic drugs (e.g., glucocorticoids). Other causes of insulin resistance are not readily apparent and require an extensive diagnostic evaluation to be identified. In general, any concurrent inflammatory, infectious, hormonal, or neoplastic disorder can cause insulin resistance and interfere with the effectiveness of insulin therapy. Identification and treatment of concurrent disease plays an integral role in the successful management of the diabetic dog. A thorough history, physical examination, and complete diagnostic evaluation are imperative in the newly-diagnosed diabetic dog (see Clinical Pathologic Abnormalities).

TECHNIQUES FOR MONITORING DIABETIC CONTROL

The basic objective of insulin therapy is to eliminate the clinical signs of diabetes mellitus while avoiding or delaying the onset of common complications associated with the disease (Box 6-6). Blindness caused by cataract formation is inevitable for most diabetic dogs but can be delayed if good glycemic control can be established and wide fluctuations in the blood glucose concentration avoided (see Cataracts). Complications to avoid include poor hair coat and unthrifty appearance, weight loss, hypoglycemia, recurring ketosis, and recurrence of polyuria and polydipsia. The devastating chronic complications of human diabetes (e.g., diabetic nephropathy, atherosclerosis) require years to develop and become clinically relevant, and are uncommon in diabetic dogs, in part, because diabetes is diagnosed in older dogs. As such, the need to establish nearly normal blood glucose concentrations is

BOX 6-6 Complications of Diabetes Mellitus

Common
Iatrogenic hypoglycemia
Persistent or recurring polyuria, polydipsia, weight loss
Cataracts
Lens-induced uveitis
Bacterial infections, especially involving the urinary tract
Chronic pancreatitis
Recurring ketosis, ketoacidosis
Hepatic lipidosis
Peripheral neuropathy
Systemic hypertension

Uncommon
Diabetic nephropathy
Significant proteinuria
Glomerulosclerosis
Retinopathy
Exocrine pancreatic insufficiency
Gastric paresis
Intestinal hypomotility and diarrhea
Diabetic dermatopathy (i.e., superficial necrolytic dermatitis)

not necessary in diabetic dogs. Most clients are happy, and most dogs are healthy and relatively asymptomatic if most blood glucose concentrations are kept between 100 mg/dL and 250 mg/dL (5.6 to 14 mmol/L).

History and Physical Examination

The most important initial parameters for assessing control of glycemia are the owner's subjective opinion of severity of clinical signs and overall health of their pet, findings on physical examination, and stability of body weight. If the owner is happy with results of treatment, the physical examination is supportive of good glycemic control, and the body weight is stable, the diabetic dog is usually adequately controlled (Briggs et al, 2000). Measurement of serum fructosamine concentration can add further objective evidence for status of glycemic control (see Serum Fructosamine Concentration). Poor control of glycemia should be suspected and additional diagnostics (i.e., serial blood glucose curve, serum fructosamine concentration, tests for concurrent disorders) or a change in insulin therapy considered if the client reports clinical signs suggestive of hyperglycemia or hypoglycemia (i.e., polyuria, polydipsia, lethargy, weakness, ataxia), the physical examination identifies problems consistent with poor control of glycemia (e.g., thin appearance, poor hair coat), or the dog is losing weight.

Single Blood Glucose Determination

Measuring a single blood glucose concentration is helpful only if hypoglycemia is identified. Documenting hypoglycemia supports insulin overdosage and the need to decrease the insulin dose, especially if glycemic control is poor. In contrast, documenting an increased blood glucose concentration does not, *by itself,* confirm poor control of glycemia. Stress or excitement can cause marked hyperglycemia, which does not reflect the dog's responsiveness to insulin and can lead to the erroneous belief that the diabetic dog is poorly controlled. If a discrepancy exists between the history, physical examination findings, and blood glucose concentration or if the dog is fractious, aggressive, excited, or scared and the blood glucose concentration is known to be unreliable, measurement of serum fructosamine concentration should be done to further evaluate status of glycemic control. In addition, a single blood glucose concentration is not reliable for evaluating the effect of a given insulin type and dose in a poorly-controlled diabetic dog.

Serum Fructosamine Concentration

Serum fructosamines are glycated proteins found in blood that are used to monitor control of glycemia in diabetic dogs and cats (Reusch et al, 1993; Crenshaw et al, 1996; Elliott et al, 1999). Fructosamines result from an irreversible, non-enzymatic, insulin-independent binding of glucose to serum proteins. Serum fructosamine concentrations 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 (Kawamoto et al, 1992). The extent of glycosylation of serum proteins is directly related to the blood glucose concentration; the higher the average blood glucose concentration during the preceding 2 to 3 weeks, the higher the serum fructosamine concentration, and vice versa. Serum fructosamine concentrations increase when glycemic control of the diabetic dog worsens and decrease when glycemic control improves. Serum fructosamine concentration is not affected by acute increases in the blood glucose concentration, as occurs with stress or excitement-induced hyperglycemia (Crenshaw et al, 1996). Serum fructosamine concentrations can be measured during the routine evaluation of the diabetic dog; to clarify the effect of stress or excitement on blood glucose concentrations; to clarify discrepancies between the history, physical examination findings, and serial blood glucose concentrations; and to assess the effectiveness of changes in insulin therapy.

Serum for fructosamine determination should be frozen and shipped on cold packs overnight to the laboratory. Although freezing does not cause a significant change in results, prolonged storage of serum at room temperature can decrease serum fructosamine results; storage of serum in the refrigerator can also decrease the serum fructosamine result (Jensen, 1992). An automated colorimetric assay using nitroblue tetrazolium chloride is used for measurement of fructosamine concentrations in serum. A linear relationship between serum total protein, albumin, and fructosamine concentration has been identified, and hypoproteinemia and hypoalbuminemia can decrease the serum fructosamine concentration below the reference range in healthy dogs and presumably diabetic dogs as well (Loste and Marca, 1999; Reusch and Haberer, 2001; Table 6-8). A decrease in serum fructosamine results has also been identified with hyperlipidemia, azotemia, hyperthyroidism (cats), and interfering substances such as hemolysis (Reusch and Haberer, 2001; Reusch and Tomsa, 1999). An increase in serum fructosamine concentration above the reference range has been identified in two dogs with hyperglobulinemia caused by multiple myeloma and in dogs with naturally-acquired hypothyroidism; an increase that decreased after initiation of sodium levothyroxine treatment (Zeugswetter et al, 2010; Reusch et al, 2002). A significant change in serum fructosamine results was not detected in healthy dogs with hyperproteinemia or hyperbilirubinemia or in healthy dogs treated with

TABLE 6-8 SAMPLE HANDLING, METHODOLOGY, AND NORMAL VALUES FOR SERUM FRUCTOSAMINE CONCENTRATIONS MEASURED IN OUR LABORATORY IN DOGS

Blood sample	1 to 2 mL serum
Sample handling	Freeze until assayed
Methodology	Automated colorimetric assay using nitroblue tetrazolium chloride
Factors affecting results	Hypoalbuminemia (decrease), hypothyroidism (increase), hyperlipidemia (mild decrease), azotemia (mild decrease), prolonged storage at room temperature (decrease), hemolysis (decrease)
Normal range	225 to 365 μmol/L
Interpretation in diabetic dogs:	
Excellent control	350 to 400 μmol/L
Good control	400 to 450 μmol/L
Fair control	450 to 500 μmol/L
Poor control	> 500 μmol/L
Prolonged hypoglycemia	< 300 μmol/L
Diabetic remission	< 300 μmol/L

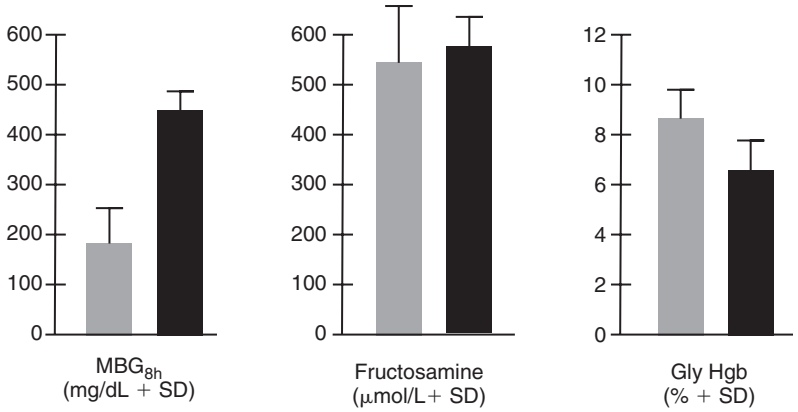

FIGURE 6-18 Mean blood glucose concentration determined over an 8-hour period *(MBG_{8h}),* serum fructosamine concentration, and blood total glycosylated hemoglobin *(Gly Hgb)* in 10 diabetic dogs with poor control of glycemia caused by the Somogyi phenomenon *(gray bars)* and 12 diabetic dogs with poor control of glycemia caused by hyperadrenocorticism-induced insulin resistance *(black bars).* Note the similar glycated protein results in both groups of dogs. Although the average blood glucose concentration is lower on the day hypoglycemia is identified in dogs with the Somogyi phenomenon, high blood glucose concentrations on subsequent days result in high glycated protein concentrations.

glucosamine-chondroitin sulfate (Lenox et al, 2010). Each laboratory should furnish its own reference range for serum fructosamine. In our laboratory, the normal reference range for serum fructosamine in dogs is 225 to 365 μmol/L, which is a range determined in healthy dogs with persistently normal blood glucose concentrations (Briggs et al, 2000). Serum fructosamine concentration in newly diagnosed diabetic dogs ranged from 320 to 850 μmol/L. The normal serum fructosamine concentration in a few diabetic dogs suggests hyperglycemia severe enough to cause clinical signs had only been present for a short time prior to diagnosis.

Interpretation of serum fructosamine in a diabetic dog must take into consideration the fact that hyperglycemia is common, even in well-controlled diabetic dogs (see Table 6-8). Most owners are happy with their pet's response to insulin treatment if serum fructosamine concentrations can be kept between 350 and 450 μmol/L. Values greater than 500 μmol/L suggest inadequate control of the diabetic state, and values greater than 600 μmol/L indicate serious lack of glycemic control. Serum fructosamine concentrations in the lower half of the reference range (i.e., < 300 μmol/L) or below the reference range should raise concern for significant periods of hypoglycemia in the diabetic dog or concurrent problems that decrease the serum fructosamine concentration (see Table 6-8). Increased serum fructosamine concentrations (i.e., > 500 μmol/L) suggest poor control of glycemia but do not identify the underlying problem (Fig. 6-18). Obtaining a serial blood glucose curve is usually the next diagnostic step to identify the problem (see Serial Blood Glucose Curve).

Serum fructosamine concentrations should not be used as the sole indicator of status of glycemic control but rather should be interpreted in conjunction with the history, findings on physical examination, and stability of body weight. A disconnect between interpretation of the serum fructosamine concentration and the clinical picture or, more commonly, results of blood glucose concentrations may occur in some diabetic dogs. When a low serum fructosamine concentration is identified in a dog with suspected poor control of the diabetic state, reasons for a low fructosamine test result (see Table 6-8) or an increase in serum glucose concentrations should be considered, and vice versa when a high serum fructosamine concentration is identified in a dog with suspected good control of the diabetic state. Whenever information used to assess glycemic control conflicts, reliance on the history, physical examination, and body weight is recommended when deciding if a change in insulin therapy is indicated.

Blood Glycated Hemoglobin Concentration

Glycated hemoglobin (Gly Hb) is a glycated protein that results from an irreversible, nonenzymatic, insulin-independent binding of glucose to hemoglobin in red blood cells. Blood Gly Hb is a marker of the average blood glucose concentration during the circulating lifespan of the red blood cell, which is approximately 110 days in the dog (Jain, 1993). The extent of glycosylation of hemoglobin is directly related to the blood glucose concentration; the higher the average blood glucose concentration during the preceding 3 to 4 months, the higher the blood Gly Hb, and vice versa. Gly Hb is used to monitor long-term effectiveness of treatment in human diabetics, in part, because diabetic humans self-monitor their blood glucose and adjust their insulin dose daily, and Gly Hb assesses a longer treatment interval than fructosamine (i.e., 3 to 4 months versus 2 to 3 weeks, respectively). In contrast, measurement of serum fructosamine is used to assess control of glycemia in diabetic dogs, in part, because the assay is readily available commercially and is better for assessing the impact of changes in insulin therapy on control of glycemia in fractious dogs because concentrations of fructosamine change more quickly than Gly Hb.

In dogs and cats, there are three fractions of Gly Hb—one major fraction (Gly HbA_{1c}) that binds glucose and two minor fractions (Gly HbA_{1a} and Gly HbA_{1b}) that do not (Hasegawa et al, 1991; 1992). Measurement of Gly HbA_{1c} is typically used to evaluate status of glycemic control in human diabetics, whereas studies in diabetic dogs have used assays that measure all three fractions—i.e., total Gly Hg (Elliott et al, 1997) or Gly HbA_{1c} (Marca et al, 2000; Marca and Loste, 2001). Most techniques that measure total Gly Hg have been shown to be clinically valid for assessing degree of diabetic control (Elliott et al, 1997; Mahaffey and Cornelius, 1982).

Gly Hb is measured in whole blood collected in ethylenediaminetetraacetic acid (EDTA). Blood samples can be refrigerated up to a week without significant change in the Gly Hb concentration.

TABLE 6-9 SAMPLE HANDLING, METHODOLOGY, AND NORMAL VALUES FOR BLOOD TOTAL GLYCOSYLATED HEMOGLOBIN CONCENTRATIONS MEASURED IN OUR LABORATORY IN DOGS

Blood sample	1 to 2 mL whole blood in EDTA
Sample handling	Refrigerate until assayed
Methodology	Affinity chromatography and hemolysates derived from canine red blood cells
Factors affecting results	Storage at room temperature (decrease); storage at 4° C for longer than 7 days (decrease); anemia (Hct < 35%) (decrease)
Normal range	1.7% to 4.9%
Interpretation in diabetic dogs:	
Excellent control	4% to 5%
Good control	5% to 6%
Fair control	6% to 7%
Poor control	> 7%
Prolonged hypoglycemia	< 4%

EDTA, Ethylenediaminetetraacetic acid; *Hct,* hematocrit.

In dogs, blood Gly Hb has been measured by affinity chromatography (Wood and Smith, 1982; Elliott et al, 1997), colorimetric analysis (Mahaffey and Cornelius, 1981), ion-exchange high performance liquid chromatography (Hasegawa et al, 1991), and immunoturbidimetric assay (Marca and Loste, 2001). Assays for measuring Gly Hb are designed for use in humans. As such, it is important that the Gly Hb assay be validated for use in the dog and that a normal reference range is established for the dog. In our experience, several Gly Hb assays, especially in-house automated analyzers for rapid measurement of Gly HbA_{1c} in human diabetics, have not provided valid results in dogs or cats. Any condition that affects red cell life span may affect Gly Hb concentration. Anemia and polycythemia can falsely decrease and increase Gly Hb concentrations, respectively (Elliott et al, 1997). The hematocrit should be taken into consideration when interpreting Gly Hb concentrations.

In our laboratory, the normal reference range for total Gly Hb as measured by affinity chromatography in dogs was 1.7% to 4.9%, which is a range determined in healthy dogs with persistently normal blood glucose concentrations (Elliott et al, 1997). Blood total Gly Hb in newly diagnosed diabetic dogs ranged from 6.0% to 15.5%. Interpretation of blood Gly Hb in a diabetic dog must take into consideration the fact that hyperglycemia is common, even in well-controlled diabetic dogs (Table 6-9). Most owners were happy with their pet's response to insulin treatment if blood total Gly Hb was kept between 4% and 6%. Values greater than 7% suggest inadequate control of the diabetic state, and values greater than 8% indicate serious lack of glycemic control. Blood total Gly Hb less than 4% should raise concern for significant periods of hypoglycemia in the diabetic dog, assuming anemia is not present. Increased total Gly Hb (i.e., > 7%) suggests poor control of glycemia but does not identify the underlying problem (see Fig. 6-18). We no longer measure Gly Hg in diabetic dogs or cats because, in our experience, blood Gly Hb did not have any diagnostic advantage over serum fructosamine determinations for assessing control of glycemia.

Urine Glucose Monitoring

Occasional monitoring of urine for glycosuria and ketonuria is helpful in diabetic dogs that have problems with recurring ketosis or hypoglycemia to identify ketonuria or persistent negative glycosuria, respectively. The client is instructed not to adjust daily insulin doses on the basis of morning urine glucose measurements, except to decrease the insulin dose in dogs with recurring hypoglycemia and persistent negative glycosuria. Many diabetic dogs develop complications because clients are misled by morning urine glucose concentrations and increase the insulin dose, which eventually results in the Somogyi response (see Insulin Overdosing and Glucose Counterregulation [Somogyi Response]). Persistent glycosuria throughout the day and night suggests inadequate control of the diabetic state and the need for a more complete evaluation of diabetic control using other techniques discussed in this section.

Serial Blood Glucose Curve

If an adjustment in insulin therapy is deemed necessary after reviewing the history, physical examination, changes in body weight, and serum fructosamine concentration, then a serial blood glucose curve should be generated to provide guidance in making the adjustment unless blood glucose measurements are unreliable because of stress, aggression, or excitement. The serial blood glucose curve provides guidelines for making rational adjustments in insulin therapy. Evaluation of a serial blood glucose curve is mandatory during the initial regulation of the diabetic dog and is necessary in the dog in which clinical manifestations of hyperglycemia or hypoglycemia have developed. Reliance on history, physical examination, body weight, and serum fructosamine concentration to determine when a serial blood glucose curve is needed help reduce the frequency of performing serial blood glucose curves, thereby minimizing the dog's aversion (and stress) to these evaluations and improving the chances of obtaining meaningful blood glucose results when a serial blood glucose curve is needed.

Protocol for Generating the Serial Blood Glucose Curve in the Hospital

When a blood glucose curve is being generated, the insulin and feeding schedule used by the client should be maintained and the dog dropped off at the hospital early in the morning. Owners of diabetic dogs who are finicky eaters should feed their pet at their home, not at the hospital. Inappetence can profoundly alter the results of a serial blood glucose curve (Fig. 6-19). The first blood sample for blood glucose measurement is obtained when the dog enters the hospital and subsequent blood samples are typically obtained every 2 hours throughout the day for glucose determination. Glucose measurements should be done more frequently than every 2 hours if the blood glucose is dropping quickly or hypoglycemia is identified. If there are concerns regarding the client's technique for administering insulin, the client can administer insulin (using his or her own insulin and syringe) in the hospital *after* the initial blood glucose is obtained or can demonstrate his or her technique using sterile saline after arriving to pick up the pet at the end of the day. The veterinarian or a veterinary technician should closely evaluate the entire insulin administration procedure. By measuring blood glucose concentration every 2 hours

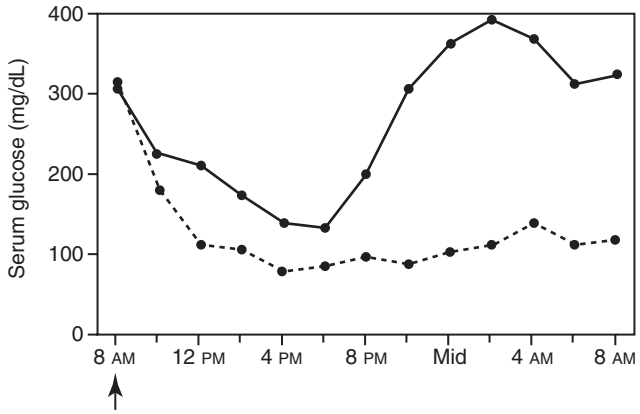

FIGURE 6-19 Mean blood glucose concentrations in eight diabetic dogs after administration of neutral protamine Hagedorn (NPH) insulin (↑) and feeding equal-sized meals at 8 AM and 6 PM *(solid line)* or feeding nothing *(broken line)* during the 24 hours of blood sampling. (From Nelson RW, Couto CG: *Essentials of small animal internal medicine,* St Louis, 1992, Mosby-Year Book, p. 572.)

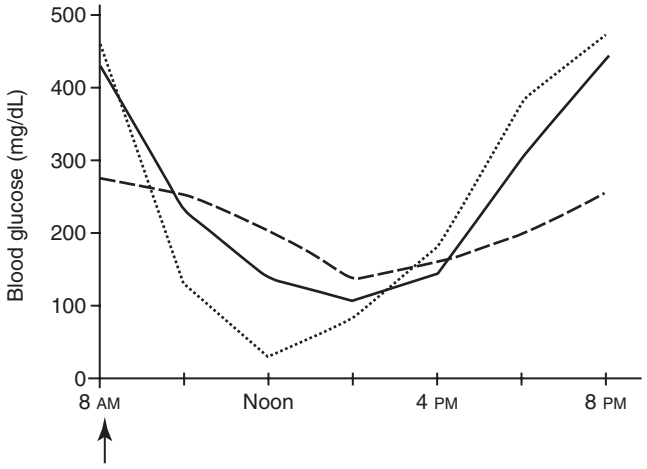

FIGURE 6-20 Blood glucose concentration curve in a Dachshund receiving 0.8 U of recombinant human Lente insulin per kilogram body weight twice a day *(solid line),* a Miniature Poodle receiving 0.6 U of recombinant human Lente insulin per kilogram body weight twice a day *(broken line),* and a Terrier-mix receiving 1.1 U of recombinant human Lente insulin per kilogram body weight twice a day *(dotted line).* Insulin and food were given at 8 AM for each dog. Interpretation of the blood glucose curves suggest short duration of insulin effect in the Dachshund, insulin underdosage in the Miniature Poodle, and the Somogyi effect in the Terrier-mix. Notice that the blood glucose concentrations were similar in all dogs at 2 PM and 4 PM, and the glucose results at these times do not establish the diagnosis in any of the dogs. (From Nelson RW, Couto CG: *Small animal internal medicine,* ed 3, St Louis, 2003, Mosby, p. 741.)

throughout the day, the clinician will be able to determine if the insulin is effective and identify the glucose nadir, time of peak insulin effect, approximate duration of insulin effect, and range of blood glucose concentrations in that particular dog. Identifying the glucose nadir and the time of the glucose nadir in relation to the time of insulin administration is critical for assessing the duration of insulin effect. If the glucose nadir has not been identified by the time of the next insulin injection, the glucose curve should be continued, the scheduled insulin injection aborted, and the dog fed its evening meal (see Prolonged Duration of Insulin Effect). Obtaining only one or two blood glucose concentrations during the day has not been reliable for evaluating the effect of a given insulin dose (Fig. 6-20). Persistent poor control of the diabetic state often stems from misinterpretation of the effects of insulin that is based on assessment of only one or two blood glucose concentrations.

Changes in blood glucose concentrations are typically assumed to be comparable following the morning and evening administration of insulin, so most dogs receive the same dose of insulin morning and evening (Mori et al, 2013). This assumption is fine as long as the dog is doing well. However, different blood glucose results during the day versus the night should be suspected if polyuria and polydipsia persist despite blood glucose concentrations that are close to acceptable during the day, especially if polyuria and polydipsia are worse at night. For these cases, obtaining a 24-hour blood glucose curve or use of a continuous glucose monitoring (CGM) device should be considered.

Blood glucose concentrations are typically determined by either a point-of-care glucose analyzer or hand-held portable blood glucose meter (PBGM) device. The accuracy of commercially available PBGM devices designed for use in human diabetics varies considerably when used in diabetic dogs, compared with results using standard reference methods (i.e., glucose oxidase and hexokinase methods) (Cohn et al, 2000; Wess and Reusch, 2000a; Cohen et al, 2009; Table 6-10). Blood glucose values determined by most PBGM devices designed for use in human diabetics are typically lower than actual glucose values determined by reference methods, and the difference between the actual glucose value and value obtained from the PBGM increases as hyperglycemia worsens (Fig. 6-21). This bias may result in an incorrect diagnosis of hypoglycemia or the misperception that glycemic control is better than it actually is. Failure to consider this error could result in insulin underdosage and the potential for persistence of clinical signs despite apparently acceptable blood glucose results. One exception is the AlphaTRAK by Abbott Laboratories, which is a PBGM device designed for use in diabetic dogs and cats. Accuracy of this PBGM device is very good, but glucose values may be higher or lower than glucose values measured by reference methodologies on the same blood sample, forcing the veterinarian to accept the blood glucose concentration at face value (Cohen et al, 2009). Hematocrit may also affect the results of PBGMs. In one study, results of the AlphaTRAK were less accurate compared with a laboratory reference method in blood samples with a lower hematocrit (< 30%) but not an increased hematocrit (> 50%), whereas results from a PBGM for use in humans was less accurate with increased hematocrit but not a decreased hematocrit (Paul et al, 2011).

Insulin therapy should be adjusted according to interpretation of a single serial blood glucose curve and the impact of the change initially assessed by client perceptions of clinical response and change in serum fructosamine concentration. If problems persist, the blood glucose curve can be repeated. If possible, performing blood glucose curves on multiple, consecutive days should be avoided, because it promotes stress-induced hyperglycemia and it takes time (several days) for derangements in hepatic glucose production and secretion to "reset." Information gained from a prior serial blood glucose curve should never be assumed to be reproducible on subsequent curves, especially if several weeks to months have passed or the dog has developed recurrence of clinical signs. The reproducibility of serial blood glucose curves varies from dog to dog. In some dogs, results of serial blood glucose curves may vary dramatically from day to day or month to month. Lack of consistency in the results of serial blood glucose curves is a source of frustration for many veterinarians. This lack of consistency is a direct reflection of all the variables that affect the blood glucose concentration in diabetics. Daily self-monitoring of blood glucose concentrations

TABLE 6-10 **BIAS ASSOCIATED WITH BLOOD GLUCOSE CONCENTRATIONS OBTAINED WITH FIVE PORTABLE BLOOD GLUCOSE METERS DESIGNED FOR HUMAN DIABETICS AND ONE METER DESIGNED FOR DIABETIC DOGS VERSUS A REFERENCE ANALYZER**

	Glucose concentration obtained with the reference analyzer (mg/dL)				
METER	**<100 N = 29**	**100-199 N = 31**	**200-299 N = 36**	**300-400 N = 36**	**> 400 N = 26**
AlphaTRAK	8 (0-28)	12 (1-44)	18 (0-99)	32 (3-110)	58 (2-179)
PBGM 1	22 (2-37)	30 (6-53)	52 (4-112)	85 (24-152)	134 (48-234)
PBGM 2	20 (12-32)	34 (18-50)	46 (0-97)	64 (1-144)	82 (30-155)
PBGM 3	30 (22-52)	54 (38-76)	81 (7-141)	95 (5-182)	102 (5-197)
PBGM 4	21 (10-52)	34 (20-54)	47 (9-104)	72 (1-136)	121 (44-196)
PBGM 5	13 (2-29)	22 (4-43)	17 (0-80)	31 (1-113)	45 (2-118)

From Cohen TA, et al.: Evaluation of six portable blood glucose meters for measuring blood glucose concentration in dogs, *J Am Vet Med Assoc* 235:276, 2009.
N, Number of blood samples; *PBGM,* portable blood glucose meter.
Data are given as median bias (range) and represent results from 158 blood samples from 49 dogs. Bias was defined as the absolute value of the difference between blood glucose results obtained with the meter and the corresponding glucose value obtained with the reference analyzer (Roche/Hitachi 917 Chemistry Analyzer).

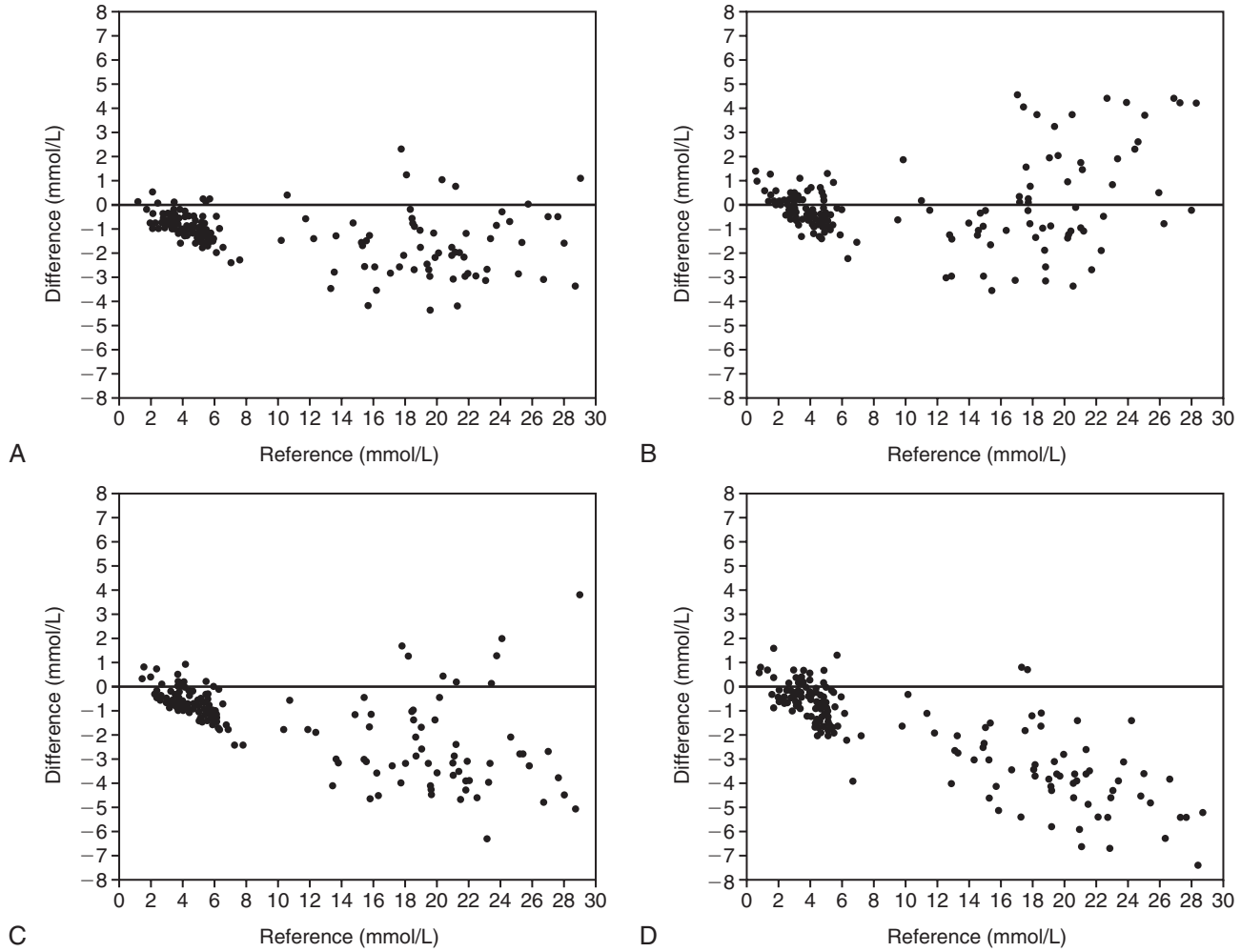

FIGURE 6-21 **A** to **D,** Scatterplots of the difference between blood glucose concentration obtained with four portable blood glucose meters and concentration obtained with a reference method versus concentration obtained with the reference method for blood samples from 170 dogs. (From Wess G, Reusch C: Evaluation of five portable blood glucose meters for use in dogs, *J Am Vet Med Assoc* 216:203, 2000.)

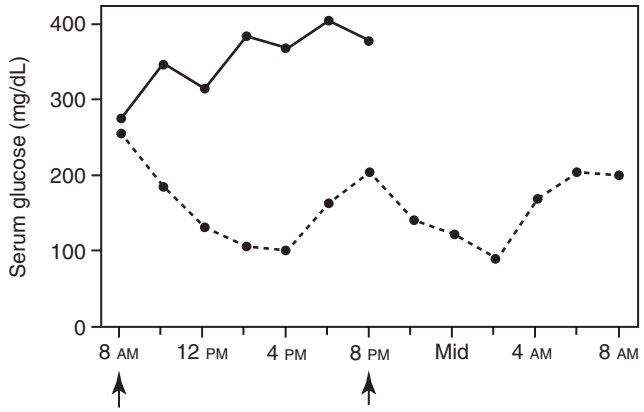

FIGURE 6-22 Blood glucose concentration curves in a fractious Terrier-mix. The same dose of neutral protamine Hagedorn (NPH) insulin was given for each curve. One glucose curve *(solid line)* was obtained with the dog in an agitated state requiring physical restraint each time a blood specimen was obtained; blood for the other glucose curve *(dotted line)* was obtained through a jugular catheter with minimal-to-no restraint and the dog in a quiet state. ↑ = Insulin administration and food.

and adjustments in insulin dose are used in human diabetics to minimize the effect of these variables on control of glycemia. A similar approach for diabetic dogs is becoming more common, as home blood glucose monitoring techniques are refined. For now, initial assessment of control of glycemia is primarily based on the client's perception of the diabetic pet's health combined with periodic examinations by the veterinarian. Serial blood glucose measurements are indicated if poor control of glycemia is suspected. The purpose of serial blood glucose measurements is to obtain a glimpse of the actions of insulin in that diabetic dog and identify a possible reason that the diabetic dog is poorly controlled.

Protocol for Generating the Serial Blood Glucose Curve at Home

Hyperglycemia induced by stress, aggression, or excitement is the single biggest problem affecting accuracy of the serial blood glucose curves (Fig. 6-22). The biggest factors causing stress-induced hyperglycemia are frequent hospitalizations and multiple venipunctures. An alternative to hospital-generated blood glucose curves is to have the client generate the blood glucose curve at home using the ear or metacarpal, metatarsal or foot pad prick technique and a PBGM device that allows the client to touch the drop of blood on the ear or foot pad with the end of the glucose test strip (Wess and Reusch, 2000b). There are several excellent websites on the Internet that demonstrate home blood glucose monitoring techniques for the owner of a diabetic dog, most notably the Abbott Laboratories website for the AlphaTRAK. This technique should be considered for diabetic dogs in which the reliability of blood glucose results generated in the veterinary hospital is questionable and is also becoming a routine monitoring technique used by clients. The biggest problem has been overzealous owners who monitor blood glucose concentrations too frequently and begin to interpret results and adjust the insulin dose without consulting their veterinarian, a practice that ultimately leads to insulin overdosage and the Somogyi response (see Fig. 6-27). See Chapter 7 for more information on home blood glucose monitoring.

Continuous Glucose Monitoring Systems

CGM systems are frequently used to monitor glucose concentrations in diabetic humans and are beginning to be used in diabetic dogs and cats (Wiedmeyer et al, 2008; Affenzeller et al, 2011). CGM systems measure interstitial fluid glucose concentrations rather than blood glucose concentrations. The correlation between interstitial and blood glucose concentrations is good in diabetic dogs and cats (Davison et al, 2003b; Moretti et al, 2010). A commonly used CGM system (Guardian REAL-time) measures interstitial glucose with a small, flexible sensor inserted through the skin into the subcutaneous space and secured to the skin (Fig. 6-23). Interstitial glucose is detected via the glucose oxidase reaction, and detection occurs entirely at the electrode within the sensor component. Glucose results are transmitted by a wireless transmitter to a pager-sized monitor. The interstitial fluid glucose concentration is recorded and stored every 5 minutes, and the data can be downloaded to a computer for analysis (Fig. 6-24). Calibration of the CGM system is required at initiation of and periodically during glucose monitoring. The working glucose range for the CGM system is 40 to 400 mg/dL (2.2 to 22 mmol/L). Studies to date suggest that the primary advantage of continuous glucose monitoring is detection of hypoglycemic periods that are not detected with serial blood glucose curves and a PBGM device (Dietiker-Moretti et al, 2011). See Chapter 7 for more information on continuous glucose monitoring.

Interpreting the Serial Blood Glucose Curve

Results of the blood glucose curve allow the veterinarian to assess the effectiveness of the administered insulin to lower the blood glucose concentration and determine the glucose nadir and the approximate duration of insulin effect (Fig. 6-25). Ideally, all blood glucose concentrations should range between 100 and 250 mg/dL (5.6 to 14 mmol/L) during the time period between insulin injections, although many diabetic dogs do well despite blood glucose concentrations consistently in the high 100s to low 300s. The goal of insulin therapy is to have the highest blood glucose concentration less than 300 mg/dL (17 mmol/L), the glucose nadir between 80 and 130 mg/dL (4.5 and 7.3 mmol/L), and the mean of all the blood glucose values measured that day to be less than 250 mg/dL (14 mmol/L). Typically, the highest blood glucose concentrations occur at the time of each insulin injection, but this does not always occur. If the blood glucose nadir is greater than 130 mg/dL, the insulin dose may need to be increased, and if the nadir is less than 80 mg/dL, the insulin dose should be decreased.

Duration of insulin effect can be assessed if the glucose nadir is greater than 80 mg/dL (4.5 mmol/L) and there has not been a rapid decrease in the blood glucose concentration after insulin administration. Assessment of duration of insulin effect may not be valid when the blood glucose decreases to less than 80 mg/dL or decreases rapidly because of the potential induction of the Somogyi response, which can falsely decrease the apparent duration of insulin effect (see Insulin Overdosing and Glucose Counterregulation [Somogyi Response]). A rough approximation of the duration of effect of insulin can be gained by examining the time of the glucose nadir. For most well-controlled diabetic dogs, the initial blood glucose concentration near the time of insulin administration is less than 300 mg/dL (17 mmol/L) and the glucose nadir occurs approximately 8 hours after injection of insulin. An initial blood glucose concentration greater than 300 mg/dL (17 mmol/L), combined with a glucose nadir occurring 6 hours or less after insulin administration and subsequent blood glucose concentrations increasing to greater than 300 mg/dL is supportive of short duration of insulin effect. A glucose nadir occurring 12 hours or longer after insulin administration is supportive of prolonged duration of insulin effect. Dogs may develop hypoglycemia or the Somogyi response if the duration of insulin effect is 14 hours or longer and the insulin is being administered twice a day (Fig. 6-26).

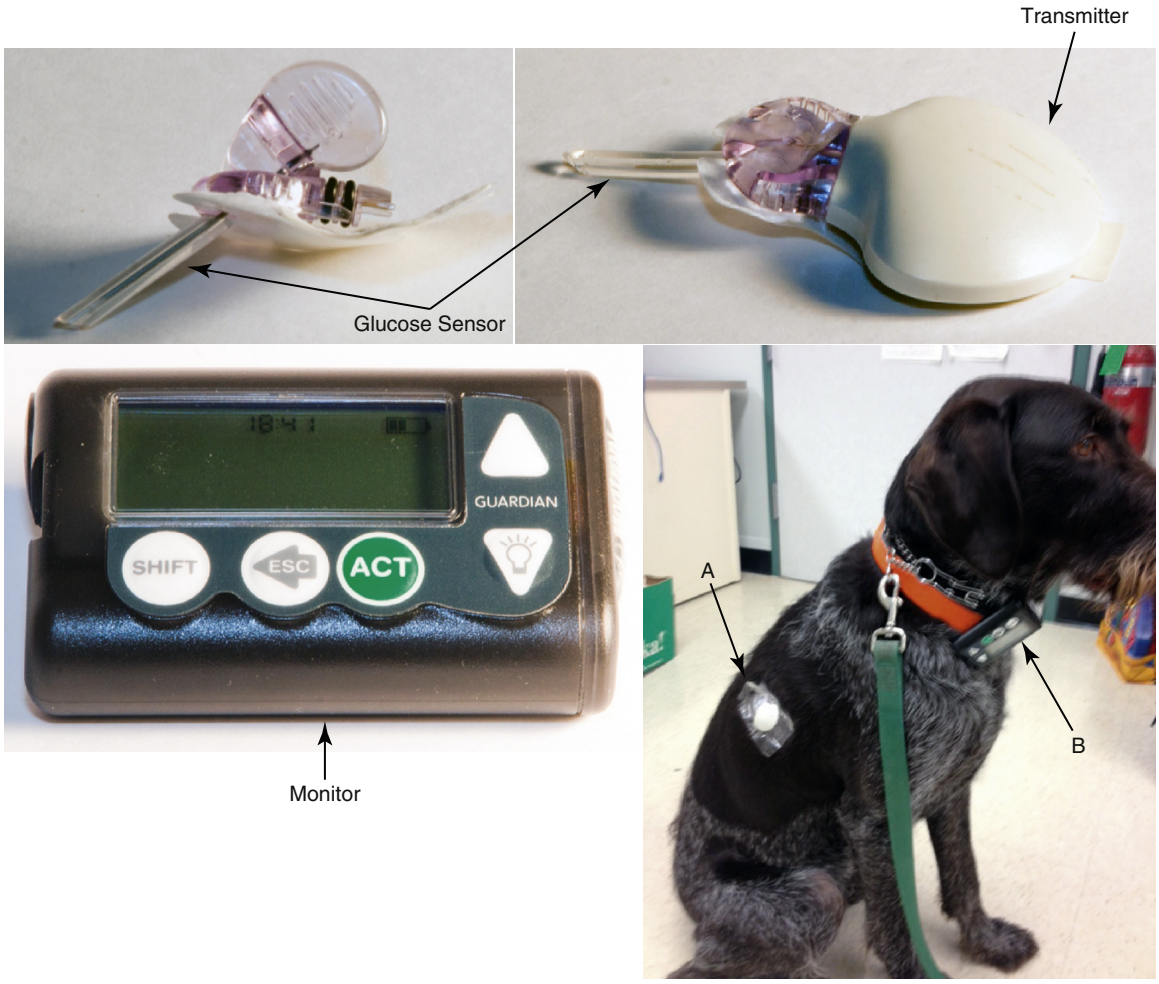

FIGURE 6-23 Guardian REAL-time continuous glucose monitor includes a small, flexible sensor that is inserted into the subcutaneous (SC) space, and interstitial glucose is measured by the glucose oxidase reaction within the sensor component. Glucose results are transmitted by a wireless transmitter to a pager-sized monitor. The interstitial fluid glucose concentration is recorded and stored every 5 minutes and the data can be downloaded to a computer for analysis. *A,* Glucose sensor and transmitter. *B,* Monitor attached to the dog's collar. The monitor can be kept in a basket next to the cage for cats.

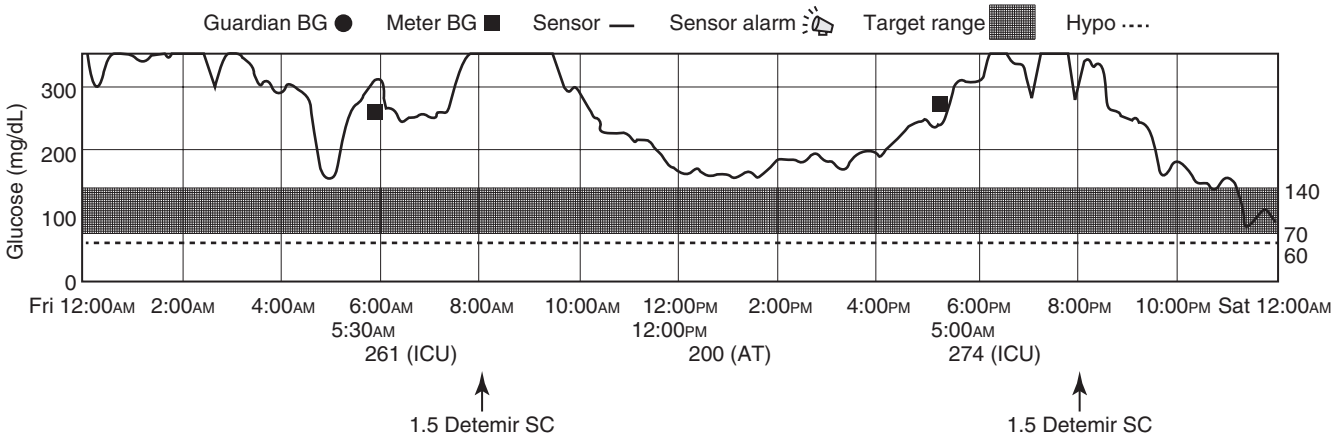

FIGURE 6-24 Example of results of continuous glucose monitoring using the Guardian REAL-time monitor in a 6 kg female-spayed diabetic Miniature Schnauzer with persistent polyuria, polydipsia, and weight loss despite various doses of insulin detemir twice daily. Hypoglycemia and possible glucose counterregulation was suspected, but blood glucose concentrations obtained by venipuncture were always increased. Stress-induced hyperglycemia was believed to be interfering with glucose results. Results of continuous glucose monitoring with minimal blood sampling documented efficacy of insulin detemir and the occurrence of hypoglycemia in the dog.

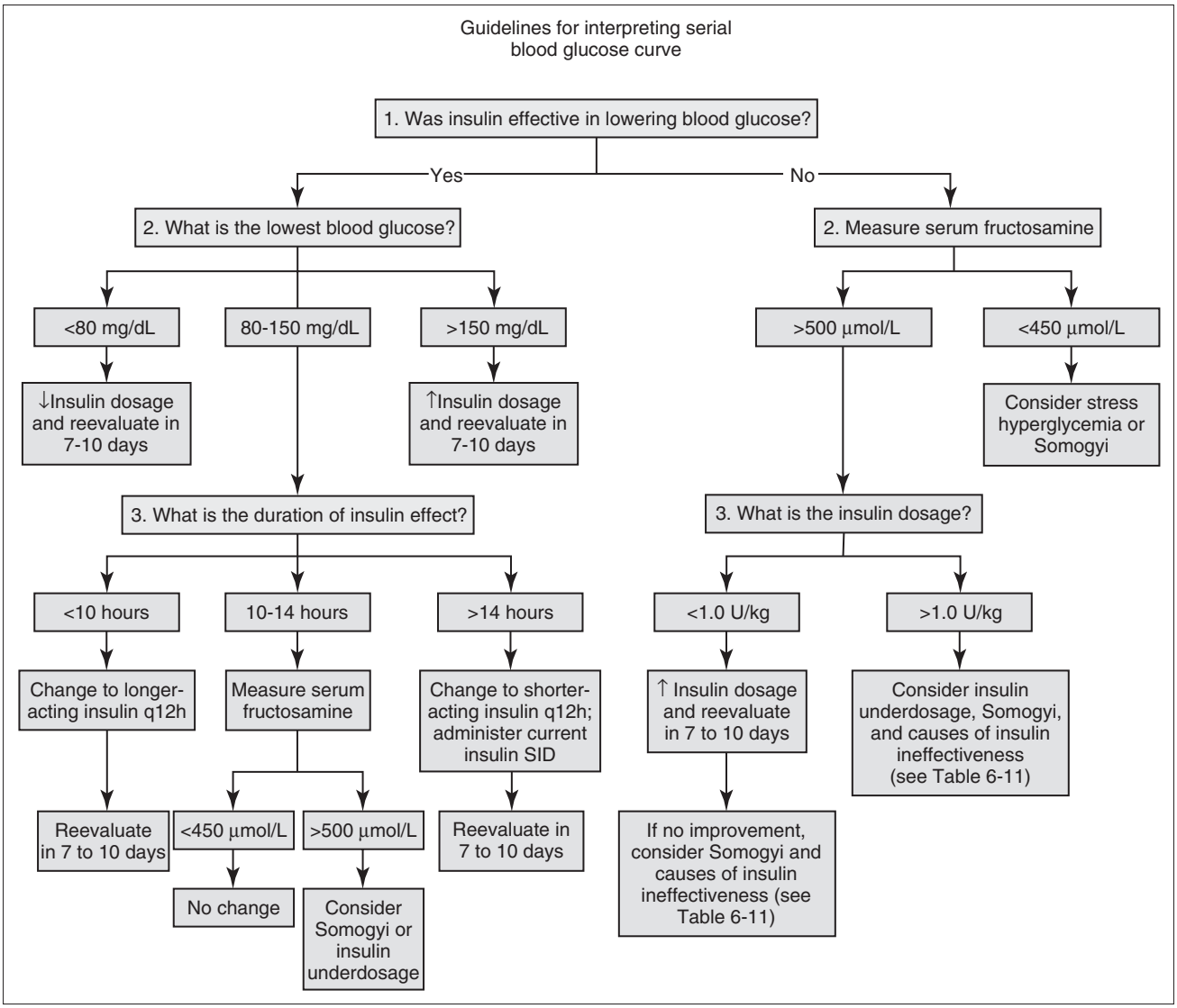

FIGURE 6-25 Algorithm for interpreting results of a serial blood glucose concentration curve. (From Nelson RW, Couto CG: *Small animal internal medicine,* ed 5, St Louis, 2014, Mosby, p. 792.)

Problems with loss of insulin activity in the bottle, insulin administration technique, insulin underdosage, and insulin resistance should be considered if the insulin is not effective in lowering the blood glucose concentration. In general, insulin underdosage should be considered if the insulin dosage is less than 1.0 U/kg per injection in the diabetic dog, and insulin resistance should be considered if the insulin dosage exceeds 1.0 U/kg per injection. The veterinarian should always be wary of the Somogyi response, especially in toy and miniature breeds, and the effect of stress on blood glucose results.

Stress Hyperglycemia

Transient hyperglycemia is a well-recognized problem in fractious, scared, or otherwise stressed cats and can also occur, albeit less frequently, in diabetic dogs. Hyperglycemia presumably develops as a result of increased catecholamine and glucocorticoid secretion and increased hepatic glucose production. Stress hyperglycemia can significantly increase blood glucose concentrations in diabetic dogs despite the administration of insulin—an effect that has serious consequences on the clinician's ability to accurately judge the effectiveness of the insulin injection. Failure to recognize the effect of stress on blood glucose results may lead to the erroneous perception that the diabetic dog is poorly-controlled; insulin therapy is invariably adjusted, often by increasing the insulin dosage; and repetition of this cycle eventually culminates in induction of the Somogyi response, clinically-apparent hypoglycemia, or referral for evaluation of insulin resistance. Stress hyperglycemia should be suspected if the dog is visibly upset, excessively nervous or hyperactive, aggressive, or difficult to restrain during the venipuncture process. Stress hyperglycemia should also be suspected when there is disparity between assessment of glycemic control based on results of the history, physical examination and stability of body weight, and assessment of glycemic control based on results of blood glucose measurements.

Role of Serum Fructosamine in Aggressive, Excitable, or Stressed Dogs

Hyperglycemia induced by stress, aggression, or excitement is the single biggest problem affecting accuracy of the serial blood glucose curve. Stress can override the glucose-lowering effect of the insulin injection, causing high blood glucose concentrations

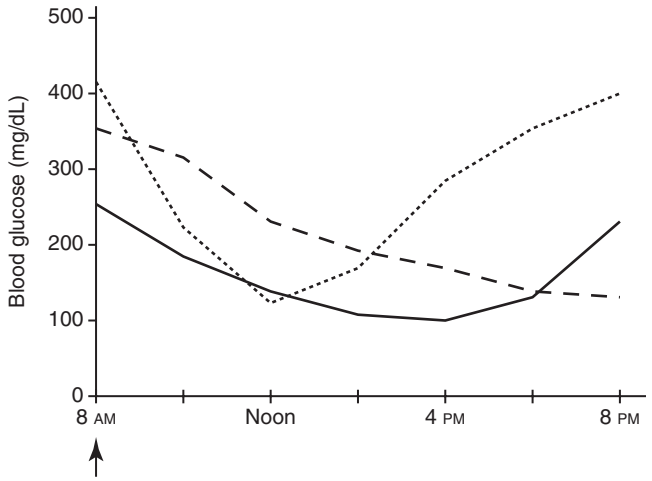

FIGURE 6-26 Blood glucose concentration curves obtained from three diabetic dogs treated with recombinant human Lente insulin twice a day, illustrating a difference between dogs in the duration of insulin effect. The insulin is effective in lowering the blood glucose concentration in all dogs, and the blood glucose nadir is between 100 and 175 mg/dL for the dogs. However, the duration of insulin effect is approximately 12 hours *(solid line)* in one dog with good control of glycemia (ideal duration of effect), approximately 8 hours *(dotted line)* in one dog with persistently poor control of glycemia (short duration of effect), and greater than 12 hours *(dashed line)* in one dog with a history of good days and bad days of glycemic control (prolonged duration of effect)—a history suggestive of the Somogyi response (see Fig. 6-28). ↑ = Insulin injection and food.

despite the presence of adequate amounts of insulin in the circulation and leading to a spiraling path of insulin overdosage, hypoglycemia, the Somogyi response, and poor control of glycemia. An alternative to hospital-generated blood glucose curves in dogs where the accuracy of blood glucose results is in question is to have the owner measure blood glucose concentrations at home as discussed previously. Alternatively, serum fructosamine concentrations can be used to assess control of glycemia and effectiveness of adjustments in insulin therapy. If a change in insulin therapy is deemed necessary, the clinician must make an educated guess as to where the problem lies (e.g., low insulin dose, short duration of insulin effect), make an adjustment in therapy, and rely on owner perception of response and the change in subsequent serum fructosamine concentration to assess the benefit of the change in treatment. Serum fructosamine concentrations should be measured prior to and 2 to 3 weeks after changing insulin therapy. If the change in insulin therapy improves control of glycemia, improvement in clinical signs and a decrease in serum fructosamine concentration of at least 50 μmol/L should occur. If the severity of clinical signs and the serum fructosamine concentration are the same or have worsened, the change was ineffective in improving glycemic control, another change in therapy should be done and the serum fructosamine measured again 2 to 3 weeks later.

INSULIN THERAPY DURING SURGERY

Generally, elective surgery should be delayed in diabetic dogs until the animal's clinical condition is stable and the diabetic state is controlled with insulin. The exception is those situations in which surgery is required to eliminate insulin resistance (e.g., ovariohysterectomy in a diestrus bitch) or to save the dog's life. The surgery itself does not pose a greater risk in a stable diabetic dog than in a non-diabetic dog. The concern is the interplay between insulin therapy and the lack of food intake during the perioperative period. The stress of anesthesia and surgery also cause the release of diabetogenic hormones, which in turn promotes ketogenesis. Insulin should be administered during the perioperative period to prevent severe hyperglycemia and minimize production of ketones. To compensate for the lack of food intake and to prevent hypoglycemia, the amount of insulin administered during the perioperative period is decreased and IV dextrose is administered, when needed. To correct marked hyperglycemia (i.e., blood glucose concentration greater than 300 mg/dL; 17 mmol/L), regular crystalline insulin is administered intramuscularly or by continuous IV infusion (see Chapter 8). Frequent blood glucose monitoring and appropriate adjustments in therapy are the key to avoiding hypoglycemia and severe hyperglycemia during the perioperative period.

We use the following protocol during the perioperative period in dogs undergoing surgery. The day before surgery, the dog is given its normal dose of insulin and fed as usual. Food is withheld after 10 PM. On the morning of the procedure, the blood glucose concentration is measured before the animal is given insulin. If the blood glucose concentration is less than 100 mg/dL (5.6 mmol/L), insulin is not given, and an IV infusion of 2.5% to 5% dextrose is initiated. If the blood glucose concentration is between 100 and 200 mg/dL (11 mmol/L), one-quarter of the animal's usual morning dose of insulin is given, and an IV infusion of dextrose is initiated. If the blood glucose concentration is more than 200 mg/dL, one-half of the usual morning dose of insulin is given, but the IV dextrose infusion is withheld until the blood glucose concentration is less than 150 mg/dL (8.4 mmol/L). In all three situations, the blood glucose concentration is measured every 30 to 60 minutes during the surgical procedure. The goal is to maintain the blood glucose concentration between 150 and 250 mg/dL (8.4 and 14 mmol/L) during the perioperative period. A 2.5% to 5% dextrose infusion is administered intravenously as needed to correct or prevent hypoglycemia. When the blood glucose concentration exceeds 300 mg/dL (17 mmol/L), the dextrose infusion should be discontinued and the blood glucose concentration evaluated 30 and 60 minutes later. If the blood glucose concentration remains greater than 300 mg/dL, regular crystalline insulin is administered intramuscularly at approximately 20% of the dose of the long-acting insulin being used at home. Subsequent doses of regular crystalline insulin should be given no more frequently than every 4 hours (6 hours if administered subcutaneously), and the dosage should be adjusted based on the effect of the first insulin injection on the blood glucose concentration.

On the day after surgery, the diabetic dog can usually be returned to the routine schedule of insulin administration and feeding. A dog that is not eating can be maintained with IV dextrose infusions and regular crystalline insulin injections given subcutaneously every 6 to 8 hours. Once the animal is eating regularly, it can be returned to its normal insulin and feeding schedule.

COMPLICATIONS OF INSULIN THERAPY

Hypoglycemia

Hypoglycemia is a common complication of insulin therapy. Signs of hypoglycemia are most apt to occur after sudden large increases in the insulin dose, with excessive overlap of insulin action in dogs receiving insulin twice a day, after prolonged inappetence, during unusually strenuous exercise, and following sudden improvement in concurrent insulin resistance. In

these situations severe hypoglycemia may occur before glucose counterregulation (i.e., secretion of glucagon, epinephrine, cortisol, and growth hormone) is able to compensate for and reverse hypoglycemia. Signs of hypoglycemia include lethargy, weakness, head tilting, ataxia, seizures, and coma. The occurrence and severity of clinical signs is dependent on the rate of blood glucose decline and the severity of hypoglycemia. Symptomatic hypoglycemia is treated with glucose administered as food, sugar water, or dextrose IV (see Chapter 9). Whenever signs of hypoglycemia occur, the owner should be instructed to stop insulin therapy until hyperglycemia and glycosuria recur. Urine glucose testing by the owner with the dog in its home environment is useful for identifying when glycosuria recurs. The adjustment in the subsequent insulin dosage is somewhat arbitrary; as a general rule of thumb, the insulin dosage initially should be decreased 25% to 50%, and subsequent adjustments in the dosage should be based on clinical response and results of blood glucose measurements. Failure of glycosuria to recur following a hypoglycemic episode is very uncommon in diabetic dogs and suggests diabetic remission (see Other Specific Types and Diabetic Remission) or impaired glucose counterregulation (see later).

In many diabetic dogs, signs of hypoglycemia are not apparent to clients, and hypoglycemia is identified during evaluation of a serial blood glucose curve or suspected when a low serum fructosamine concentration is identified. Failure to identify hypoglycemia during a blood glucose curve or low-normal serum fructosamine concentration does not rule out asymptomatic hypoglycemia, in part, because of hypoglycemia-induced glucose counterregulation (Somogyi response). Clinical signs of hyperglycemia, transient asymptomatic hypoglycemia, and high serum fructosamine concentrations dominate the clinical picture in diabetic dogs with the Somogyi response.

Treatment of asymptomatic hypoglycemia involves decreasing the dose of insulin (typically 10% to 20%) and assessing the clinical response, change in serum fructosamine concentration, and blood glucose concentrations. If hypoglycemia remains a reoccurring problem despite reductions in the insulin dose, problems with prolonged duration of insulin effect should be considered.

Impaired Glucose Counterregulation

Secretion of the diabetogenic hormones, most notably epinephrine and glucagon, stimulates hepatic glucose secretion and helps counter severe hypoglycemia. A deficient counterregulatory response to hypoglycemia has been identified as early as 1 year after diagnosis of type 1 diabetes in humans (White et al, 1983). As a consequence, when the blood glucose concentration approaches 60 mg/dL (3.4 mmol/L), there is no compensatory response by the body to increase the blood sugar, and prolonged hypoglycemia ensues. An impaired counterregulatory response to hypoglycemia has also been documented in diabetic dogs (Duesberg et al, 1995). Dogs with impaired counterregulation had more problems with hypoglycemia than diabetic dogs without impaired counterregulation. Impaired counterregulation should be considered in a diabetic dog exquisitely sensitive to small doses of insulin or with problems of prolonged hypoglycemia after administration of an acceptable dose of insulin.

Inappetence

A healthy, well-regulated diabetic dog should maintain an excellent appetite. Occasional inappetence at mealtime is not, by itself, an indication to stop insulin therapy. Most diabetic dogs eat within a couple of hours of the insulin injection, as the blood glucose begins to decline. If the inappetence persists or if other signs of gastrointestinal dysfunction develop (e.g., vomiting), insulin therapy should be modified or discontinued until the veterinarian has examined the dog. Common causes of inappetence in diabetic dogs include pancreatitis, ketoacidosis, hepatopathy, inflammatory bowel disease, bacterial infection, finicky eaters, and boredom with high fiber diets. Appropriate diagnostic and therapeutic steps should be initiated, depending on results of the physical examination.

Recurrence or Persistence of Clinical Signs

Recurrence or persistence of clinical signs (i.e., polyuria, polydipsia, polyphagia, weight loss) is perhaps the most common complication of insulin therapy in diabetic dogs. Recurrence or persistence of clinical signs is usually caused by problems with biologic activity of the insulin or with owner technique in administering insulin; problems with the insulin treatment regimen; or problems with responsiveness to insulin caused by concurrent inflammatory, infectious, neoplastic, or hormonal disorders (i.e., insulin resistance). The most common problems with the insulin treatment regimen in the dog include insulin underdosage, induction of the Somogyi response, short duration of effect of Lente or NPH insulin, and once a day insulin administration. Discrepancies in the parameters used to assess glycemic control, resulting in an erroneous belief that the diabetic dog is poorly controlled, should also be considered. This is usually caused by erroneously high blood glucose concentrations induced by stress that suggest insulin ineffectiveness or presence of a concurrent unrecognized disorder that also causes polyuria and polydipsia, such as early renal insufficiency. When evaluating a diabetic dog for suspected insulin ineffectiveness, it is important that all parameters used to assess glycemic control be critically analyzed, most notably the owners' perceptions of how their dog is doing in the home environment, findings on physical examination, and changes in body weight. If the history, physical examination, change in body weight, and serum fructosamine concentration suggest poor control of the diabetic state, a diagnostic evaluation to identify the cause is warranted, beginning with evaluation of the owner's insulin administration technique and the biologic activity of the insulin preparation.

Problems with Owner Administration and Activity of the Insulin Preparation

Failure to administer an appropriate dose of biologically active insulin results in recurrence or persistence of clinical signs. Common reasons include administration of biologically inactive insulin (e.g., outdated, previously heated or frozen; see Insulin Storage, Mixing, and Dilution), administration of diluted insulin, use of inappropriate insulin syringes for the concentration of insulin (e.g., U100 syringe with U40 insulin), or problems with insulin administration technique (e.g., failure to correctly read the insulin syringe, inappropriate injection technique). These problems are identified by evaluating the client's insulin administration technique and by administering new, undiluted insulin and measuring several blood glucose concentrations throughout the day. In addition, the skin and subcutaneous tissues should be assessed in the area where insulin injections are given. Some diabetic dogs develop low-grade inflammation, edema, and thickening of the dermis and subcutaneous tissues in areas of chronic insulin administration and these changes can interfere with insulin absorption following subcutaneous administration (see Allergic Reactions to Insulin).

Problems with the Insulin Treatment Regimen

The most common problems causing poor control of glycemia in this category include insulin underdosage, the Somogyi phenomenon, short duration of effect of Lente and NPH insulin, and once a day insulin administration. The insulin treatment regimen should be critically evaluated for possible problems in these areas, and appropriate changes should be made to try to improve insulin effectiveness, especially if the history and physical examination do not suggest a concurrent disorder causing insulin resistance.

Insulin Underdosage

Control of glycemia can be established in most dogs using 1.0 U or less of insulin/kg of body weight administered twice each day (see Table 6-7). An inadequate dose of insulin in conjunction with once a day insulin therapy is a common cause for persistence of clinical signs. In general, insulin underdosing should be considered if the insulin dosage is less than 1.0 U/kg and the dog is receiving insulin twice a day. If insulin underdosing is suspected, the dose of insulin should be gradually increased by 1 to 5 U/injection (depending on the size of the dog) per week. The effectiveness of the change in therapy should be evaluated by client perception of clinical response and measurement of serum fructosamine or serial blood glucose concentrations. Although some dogs require insulin dosages as high as 1.5 U/kg to attain control of glycemia, other causes for insulin ineffectiveness, most notably the Somogyi response and concurrent insulin resistance, should be considered once the insulin dose exceeds 1.0 U/kg/injection, the insulin is being administered every 12 hours, and control of glycemia remains poor.

Insulin Overdosing and Glucose Counterregulation (Somogyi Response)

The Somogyi response results from a normal physiologic response to impending hypoglycemia induced by excessive insulin. When the blood glucose concentration declines to less than 65 mg/dL (3.6 mmol/L) or when the blood glucose concentration decreases rapidly regardless of the glucose nadir, direct hypoglycemia-induced stimulation of hepatic glycogenolysis and secretion of diabetogenic hormones (most notably epinephrine and glucagon) increase the blood glucose concentration, minimize signs of hypoglycemia, and cause marked hyperglycemia within 12 hours of glucose counterregulation. The marked hyperglycemia that occurs after hypoglycemia is due, in part, to an inability of the diabetic dog to secrete sufficient endogenous insulin to dampen the rising blood glucose concentration in conjunction with insufficient concentrations of circulating insulin derived from the injected insulin (Fig. 6-27; see Hypoglycemia and the Counterregulatory Response in Chapter 9; Cryer and Polonsky, 1998; Karam, 2001). By the next morning, the blood glucose concentration can be extremely elevated (greater than 400 mg/dL; 22 mmol/L), and the morning urine glucose concentration is consistently 1 to 2 gm/dL as measured with urine glucose test strips.

Unrecognized short duration of insulin effect combined with insulin dose adjustments based on morning urine glucose concentrations is historically the most common cause for the Somogyi response in dogs. Currently, the most common cause for the Somogyi response are clients who monitor their pet's blood glucose concentration at home and adjust the insulin dose (i.e., increase the dose) without consulting their veterinarian. The increasing use of longer-acting insulin preparations (i.e., insulin glargine, insulin detemir) that have the potential to last longer than 12 hours may dampen the severity of the post-hypoglycemic hyperglycemia historically affiliated with the Somogyi response, presumably because insulin derived from the injected insulin is still present in the circulation. The diabetogenic hormonal response to hypoglycemia is still intact, and persistently increased concentrations of these hormones will still negatively impact control of glycemia, especially if hypoglycemia and the diabetogenic hormonal response reoccur frequently.

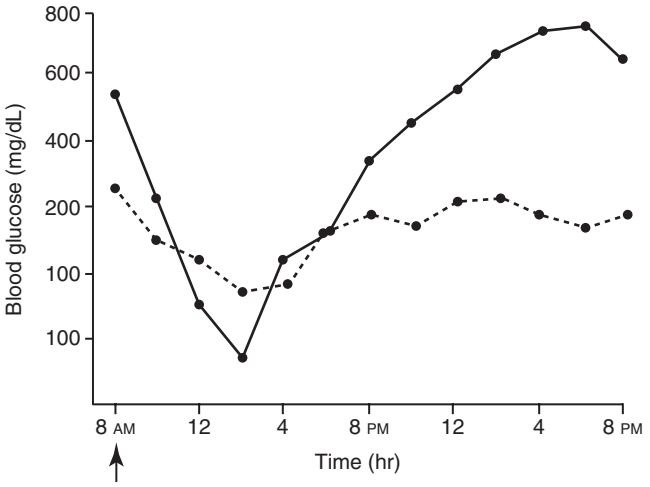

FIGURE 6-27 Blood glucose concentrations in a 6.1 kg Cairn terrier after receiving beef/pork source neutral protamine Hagedorn (NPH) insulin at 8 AM. The dog was fed at 8 AM and 6 PM. *Solid line,* 20 units; *broken line,* 4 units; (From Feldman EC, Nelson RW: Insulin-induced hyperglycemia in diabetic dogs, *J Am Vet Med Assoc* 180:1432, 1982.) ↑ = insulin injection.

Clinical signs of hypoglycemia are typically mild or not recognized by the client; clinical signs caused by hyperglycemia tend to dominate the clinical picture. The insulin dose that induces the Somogyi response is variable and unpredictable. The Somogyi response should be suspected in poorly-controlled diabetic dogs in which insulin dosage exceeds 1.0 U/kg body weight/injection but can also occur at insulin dosages less than 0.5 U/kg/injection (see Table 6-7). Toy and miniature breeds of dogs are especially susceptible to development of the Somogyi response with lower-than-expected doses of insulin. The Somogyi response should always be suspected in any poorly-controlled diabetic dog, regardless of the amount of insulin being administered. Induction of the Somogyi response typically leads to high insulin doses as the veterinarian reacts to the persistence of clinical signs, absence of clinical hypoglycemia, and high blood glucose and serum fructosamine concentrations by increasing the insulin dose and perpetuating the problem.

The diagnosis of the Somogyi response requires demonstration of hypoglycemia (less than 65 mg/dL; 3.6 mmol/L) followed by hyperglycemia (greater than 300 mg/dL; 17 mmol/L) after insulin administration (Feldman and Nelson, 1982; Fig. 6-28). The Somogyi response should also be suspected when the blood glucose concentration decreases rapidly regardless of the glucose nadir (e.g., a drop from 400 to 100 mg/dL [22 to 5.6 mmol/L] in 2 to 3 hours). If the duration of insulin effect is greater than 12 hours, hypoglycemia often occurs at night after the evening dose of insulin, and the serum glucose concentration is typically greater than 300 mg/dL the next morning. Unfortunately, the diagnosis of the Somogyi response can be elusive, in part because of the effects of the diabetogenic hormones on blood glucose concentrations after an episode of glucose counterregulation.

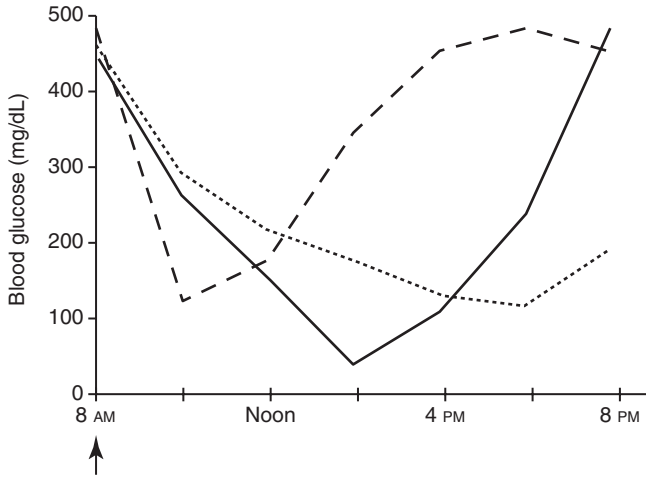

FIGURE 6-28 Blood glucose concentration curves obtained from three poorly-controlled diabetic dogs treated with recombinant human Lente insulin twice a day, illustrating the typical blood glucose curves suggestive of the Somogyi response. In one dog *(solid line)* the glucose nadir is less than 80 mg/dL and is followed by a rapid increase in the blood glucose concentration. In one dog *(dashed line)* a rapid decrease in the blood glucose concentration occurs within 2 hours of insulin administration and is followed by a rapid increase in the blood glucose concentration; the rapid decrease in blood glucose stimulates glucose counterregulation, despite maintaining the blood glucose nadir above 80 mg/dL. In one dog *(dotted line)* the blood glucose curve is not suggestive of the Somogyi response, per se. However, the insulin injection causes the blood glucose to decrease by approximately 300 mg/dL during the day, and the blood glucose concentration at the time of the evening insulin injection is considerably lower than the 8 am blood glucose concentration. If a similar decrease in the blood glucose occurs with the evening insulin injection, hypoglycemia and the Somogyi response would occur at night and would explain the high blood glucose concentration in the morning and the poor control of the diabetic state. (From Nelson RW, Couto CG: *Small animal internal medicine,* ed 5, St Louis, 2014, Mosby, p. 794.) ↑ = Insulin injection and food.

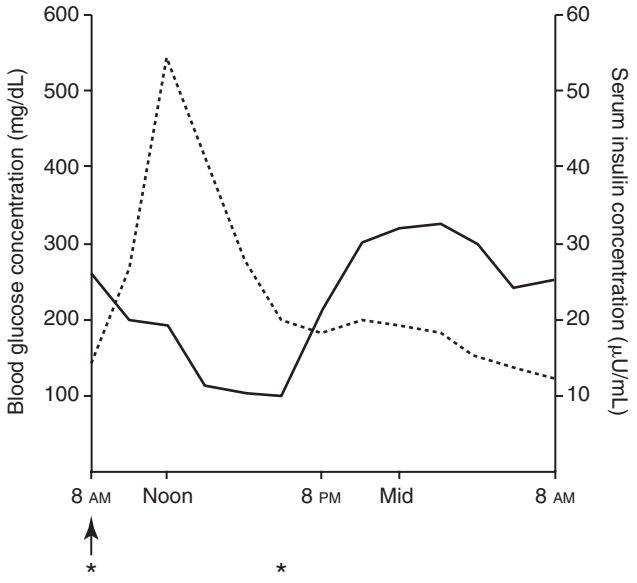

FIGURE 6-29 Mean blood glucose *(solid line)* and serum insulin *(dotted line)* concentrations in eight dogs with diabetes mellitus treated with a beef/pork source neutral protamine Hagedorn (NPH) insulin subcutaneously once daily. The duration of NPH effect is too short, resulting in prolonged periods of hyperglycemia beginning shortly after the evening meal. (From Nelson RW, Couto CG: *Small animal internal medicine,* ed 5. St Louis, 2014, Mosby, p. 795.) ↑ = Insulin injection; * = equal-sized meals consumed.

Secretion of diabetogenic hormones during the Somogyi response may induce insulin resistance, which can last 24 to 72 hours after the hypoglycemic episode. If a serial blood glucose curve is obtained on the day glucose counterregulation occurs, hypoglycemia will be identified and the diagnosis established. However, if the serial blood glucose curve is obtained on a day when insulin resistance predominates, hypoglycemia will not be identified and the insulin dose may be incorrectly increased in response to the high blood glucose values. A cyclic history of 1 or 2 days of good glycemic control followed by several days of poor control should raise suspicion for insulin resistance caused by glucose counterregulation. Serum fructosamine concentrations are unpredictable but are usually increased >500 μmol/L, results that confirm poor glycemic control but do not identify the underlying cause (see Fig. 6-18).

Establishing the diagnosis may require several days of hospitalization and serial blood glucose curves, an approach that eventually leads to problems with stress-induced hyperglycemia. An alternative, preferable approach is to arbitrarily gradually reduce the insulin dose 1 to 5 units (depending on the size of the dog and dose of insulin) and have the client evaluate the dog's clinical response over the ensuing 2 to 5 days, specifically as it relates to changes in polyuria and polydipsia. If the severity of polyuria and polydipsia worsens after an initial reduction in the insulin dose, another cause for the insulin ineffectiveness should be pursued. However, if the client reports no change or improvement in polyuria and polydipsia, continued gradual reduction of the insulin dose should be pursued until polyuria and polydipsia worsen again, which identifies an inadequate dose of insulin for the dog. Alternatively, glycemic regulation of the diabetic dog could be started over using an insulin dose of 0.25 U/kg given twice daily.

Short Duration of Insulin Effect

For most dogs, the duration of effect of recombinant human Lente and NPH insulin is 10 to 14 hours, and twice a day insulin administration is effective in controlling blood glucose concentrations. However, in some diabetic dogs, the duration of effect of Lente and NPH insulin is less than 10 hours; a duration that is too short to prevent periods of hyperglycemia and persistence of clinical signs (Fig. 6-29; see Fig. 6-14). Diabetic dogs with the problem of short duration of insulin effect have persistent morning glycosuria (> 1 g/dL on urine glucose test strips) regardless of the insulin dose being administered. Owners of these pets usually mention continuing problems with evening polyuria and polydipsia, or weight loss. If owners are adjusting the daily insulin dosage based on the morning urine glucose concentration, they usually induce the Somogyi response as the insulin dosage is gradually increased in response to persistent morning glycosuria. Serum fructosamine concentrations are variable but typically greater than 500 μmol/L. A diagnosis of short duration of insulin effect is made by demonstrating an initial blood glucose concentration greater than 300 mg/dL combined with a glucose nadir above 80 mg/dL (4.5 mmol/L) that occurs less than 8 hours after insulin administration and recurrence of hyperglycemia (greater than 300 mg/dL; 17 mmol/L) within 12 hours of the insulin injection (see Fig. 6-26). Diabetic dogs that have a short duration of insulin effect can be diagnosed only by determining serial blood glucose

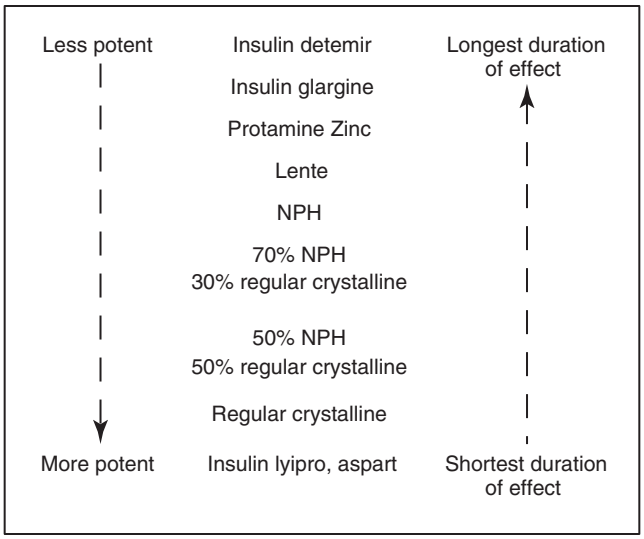

FIGURE 6-30 Types of commercial insulin based on their potency and duration of effect. An inverse relationship exists between the potency and duration of effect. (From Nelson RW, Couto CG: *Small animal internal medicine,* ed 5, St Louis, 2014, Mosby, p. 793.)

concentrations. One or two afternoon blood glucose determinations consistently fail to identify the problem. They may identify normal glucose concentrations or mild hyperglycemia, findings that are not consistent with the worries of the owner and do not identify the underlying problem. Alternatively, one or two afternoon blood glucose determinations may reveal severe hyperglycemia, findings that do not differentiate short duration of insulin effect from the Somogyi response or insulin resistance. Treatment involves changing to a longer-acting insulin (Fig. 6-30). Although PZI, insulin glargine, and insulin detemir all have the potential to be effective in diabetic dogs, my preference is to switch to insulin detemir when Lente and NPH are ineffective because of short duration of insulin effect. Insulin detemir is a potent insulin with the potential for prolonged duration of effect (greater than 14 hours), which can create issues with hypoglycemia and the Somogyi response when insulin detemir is given twice a day. Regardless, most diabetic dogs require insulin detemir twice a day to attain diabetic control, recognizing that the insulin dosage can be quite small to compensate for the potency and prolonged duration of effect of the insulin. The recommended starting dosage for insulin detemir is 0.1 U/kg administered every 12 hours.

Prolonged Duration of Insulin Effect

In some diabetic dogs, the duration of effect of Lente and NPH insulin is greater than 12 hours, and twice a day insulin administration creates problems with hypoglycemia and the Somogyi response. In these dogs, the glucose nadir following the morning administration of insulin typically occurs near or after the time of the evening insulin administration, and the morning blood glucose concentration is usually greater than 300 mg/dL (17 mmol/L) (see Fig. 6-26). Gradually decreasing blood glucose concentrations measured at the time of sequential insulin injections is another indication of prolonged duration of insulin effect. The effectiveness of insulin in lowering the blood glucose concentration is variable from day to day, presumably because of varying concentrations of diabetogenic hormones whose secretion was induced by prior hypoglycemia. Serum fructosamine concentrations are variable but typically greater than 500 µmol/L. An effective treatment depends, in part, on the duration of effect of the insulin. An extended blood glucose curve should be generated after administration of insulin once in the morning and feeding the dog at the normal times of the day. This allows the clinician to evaluate the effect of the evening meal on postprandial blood glucose concentrations and estimate whether insulin from the morning injection is still present in the blood and capable of preventing a postprandial increase in the blood glucose. If the postprandial blood glucose increases (typically 75 mg/dL [4.2 mmol/L] or more) within 2 hours of feeding, the duration of effect is close to 12 hours and manipulation of the insulin dose, the timing of the meals in relation to the timing of the insulin injections, or both, should be tried before switching to a longer acting insulin. Failure of the blood glucose to increase 2 hours or longer after eating the evening meal suggests a prolonged duration of effect (i.e., longer than 14 hours). Switching to a longer acting insulin (e.g., insulin detemir) administered once a day can be tried initially (see Fig. 6-30).

Inadequate Insulin Absorption

Slow or inadequate absorption of insulin from the subcutaneous site is uncommon in diabetic dogs treated with NPH or Lente insulin. Impaired absorption of insulin may occur as a result of thickening of the skin and inflammation of the subcutaneous tissues caused by chronic injection of insulin in the same area of the body (see Allergic Reactions to Insulin). Rotation of the injection site helps prevent this problem, and avoidance of regions that have become thickened should improve insulin absorption.

Circulating Insulin-Binding Antibodies

Insulin antibodies result from repeated injections of a foreign protein (i.e., insulin). The structure and amino acid sequence of the injected insulin relative to the native endogenous insulin influence the development of insulin antibodies. The presence of substances in the insulin preparation designed to prolong insulin effect (e.g., protamine) may also play a role in inducing antibody formation (Kurtz et al, 1983). Conformational insulin epitopes are believed to be more important in the development of insulin antibodies than differences in the linear subunits of the insulin molecule, per se (Thomas et al, 1985; 1988; Nell and Thomas, 1989; Davison et al, 2008b). The more divergent the insulin molecule being administered from the species being treated is, the greater the likelihood that significant amounts of insulin antibodies will be formed. Canine, porcine, and recombinant human insulin are similar, and development of a clinically relevant amount of insulin antibodies is uncommon in dogs treated with porcine or recombinant human insulin. In contrast, canine and beef insulin differ and serum insulin antibodies have been identified in 40% to 65% of dogs treated with beef/pork or beef insulin (Haines, 1986; Davison et al, 2008b).

Insulin-binding antibodies can enhance and prolong the pharmacodynamic action of insulin by serving as a carrier, or they can reduce insulin action by excessive binding and reduction of circulating unbound "free" insulin (Bolli et al, 1984; Marshall et al, 1988; Lahtela et al, 1997). Antibodies may also have no apparent clinical effect on insulin dosage or status of glycemic control (Lindholm et al, 2002). In our experience, the presence of significant amounts of insulin-binding antibodies is associated with erratic and often poor control of glycemia, an inability to maintain control of glycemia for extended periods of time, frequent adjustments in insulin dose, and occasional development of severe insulin resistance (Fig. 6-31). Insulin-binding antibodies can also

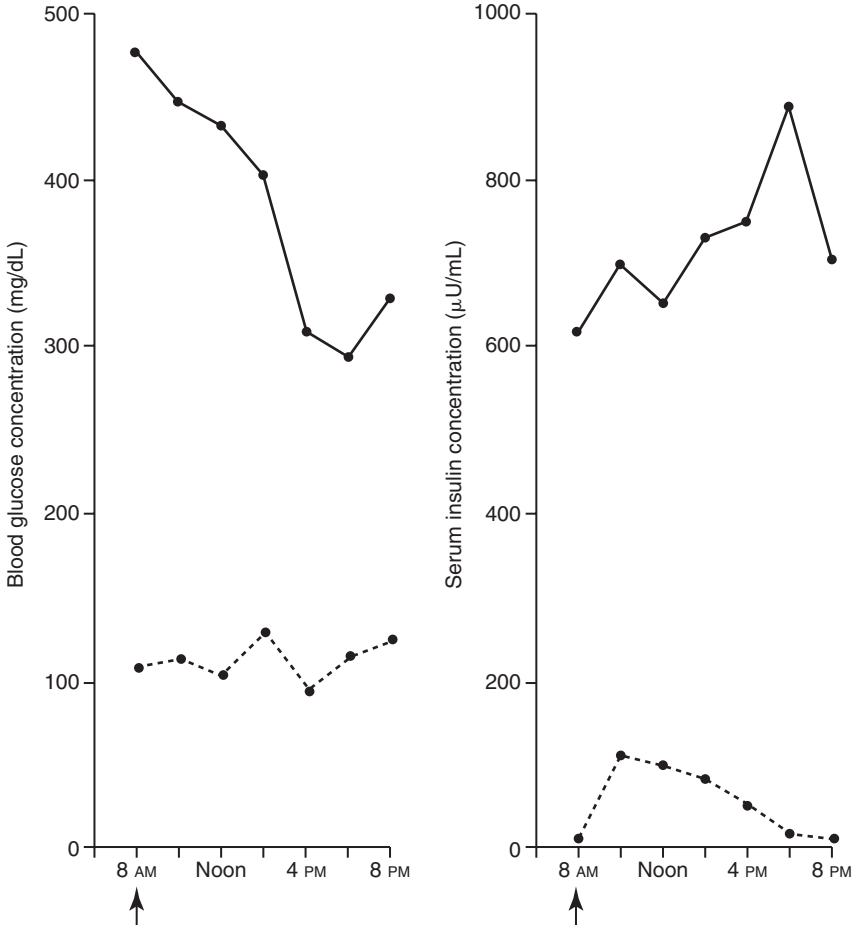

FIGURE 6-31 Blood glucose and serum insulin concentrations in a 7.6 kg, spayed dog receiving 1.1 U/kg beef/pork source Lente insulin (solid line) subcutaneously. The dog had severe polyuria, polydipsia, and weight loss. A baseline serum insulin concentration was greater than 1000 μU/mL 48 hours after discontinuing insulin therapy. Interference from anti-insulin antibodies was suspected, and the source of insulin was changed to recombinant human insulin. Clinical signs improved within 2 weeks, and a blood glucose curve was obtained 4 weeks later with the dog receiving 0.9 U/kg recombinant human Lente insulin (broken line), showed excellent glycemic control. Presumably, loss of anti-insulin antibody interference with the insulin radioimmunoassay (RIA) allowed a more accurate assessment of changes in the serum insulin concentration after recombinant human insulin administration. (From Nelson RW, Couto CG: *Small animal internal medicine,* ed 5. St Louis, 2014, Mosby, p. 795.) ↑ = Insulin injection and food.

cause erratic fluctuations in the blood glucose concentration with no correlation between the timing of insulin administration and changes in blood glucose concentration (Fig. 6-32). Presumably, fluctuations in blood glucose concentration result from erratic and unpredictable changes in the circulating free (i.e., non–antibody-bound) insulin concentration (Bolli et al, 1984). This phenomenon causes inappropriate and potentially life-threatening hypoglycemia at unexpected times in human diabetics. We have observed a similar syndrome in diabetic dogs treated with beef/pork insulin preparations. Problems with glycemic control typically improve or resolve with the initiation of porcine-source or recombinant human insulin preparations. Although uncommon, insulin antibodies can develop in dogs treated with recombinant human insulin and should be suspected as the cause of poor glycemic control when another cause cannot be identified.

Documentation of serum insulin-binding antibodies should make use of assays that have been validated in diabetic dogs. A radioimmunoassay (RIA) for identifying insulin antibodies in dogs is currently available at the Diagnostic Center for Population and Animal Health, Michigan State University, East Lansing, Mich. Although the finite range of possible results with this assay is 0% to 100%, normal results are typically 15% or less and significant positive results are greater than 40% to 50%.

Circulating insulin-binding antibodies may interfere with some RIA techniques used to measure serum insulin concentration in a manner similar to the effects of thyroid hormone antibodies on RIA techniques for serum triiodothyronine (T_3) and T_4 concentrations (see Chapter 3). The presence of insulin-binding antibodies in the serum sample causes spuriously high insulin values when a single-phase separation system utilizing antibody-coated tubes is used to measure serum insulin concentration. This interference can be used to raise the clinician's index of suspicion for insulin-binding antibodies as a cause for insulin resistance. The serum insulin concentration is typically less than 50 μU/mL (360 pmol/L) 24 hours after insulin administration in diabetic dogs without antibodies causing interference with the RIA. In contrast, serum insulin concentrations are typically greater than 400 μU/mL (2800 pmol/L) 24 hours after insulin administration when insulin-binding antibodies interfere with the RIA results—an interaction that causes spurious results (see Fig. 6-31).

A switch to porcine-source or recombinant human insulin preparation, a switch to an insulin preparation that does not contain protamine, or both should be considered if insulin-binding antibodies are identified in a poorly-controlled diabetic dog. Studies evaluating the antigenicity of insulin analogues (i.e., glargine, detemir) in diabetic dogs have not yet been reported. In our experience, insulin antibody results greater than 15% using the Michigan State University insulin antibody assay are uncommon in diabetic dogs treated with insulin analogues.

Allergic Reactions to Insulin

Significant reactions to insulin occur in as many as 5% of human diabetics treated with insulin and include erythema, pruritus, induration, and lipoatrophy at the injection site. Allergic reactions to insulin have been poorly documented in diabetic dogs. Pain on injection of insulin is usually caused by inappropriate injection

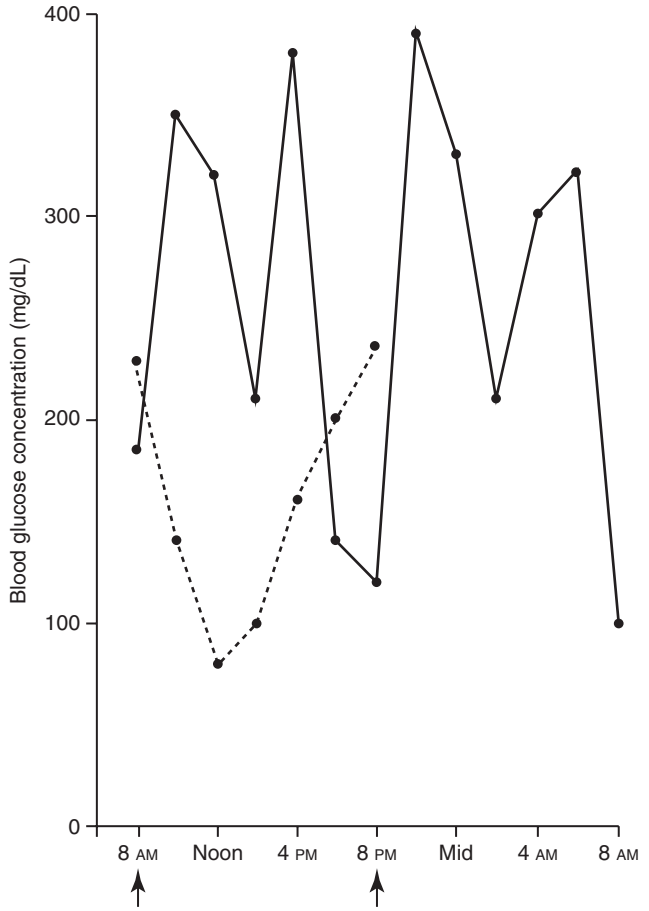

FIGURE 6-32 Blood glucose curve in a 50 kg male dog receiving 0.7 U/kg beef/pork source Lente insulin *(solid line)* subcutaneously. Note the erratic fluctuations in the blood glucose concentration. The dog had polyuria, polydipsia, and weight loss and was blind from cataract formation. A baseline serum insulin concentration was 825 μU/mL 24 hours after discontinuing insulin therapy. Interference from anti-insulin antibodies was suspected, and the source of insulin was changed to recombinant human insulin. Clinical signs improved within 1 month, and a blood glucose curve was obtained 8 weeks later with the dog receiving 0.5 U/kg recombinant human Lente insulin *(broken line),* showing excellent glycemic control and loss of erratic fluctuations in the blood glucose concentration.

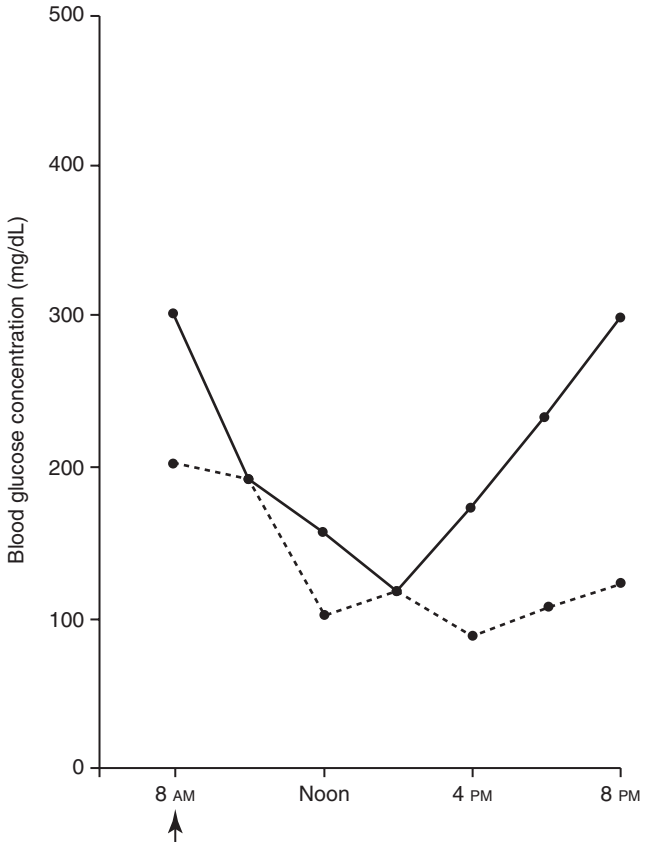

FIGURE 6-33 Blood glucose curve in a 12 kg male diabetic dog with untreated hypothyroidism receiving 2.2 U/kg recombinant human Lente insulin *(solid line).* The large amount of insulin required to lower the blood glucose concentration suggests insulin resistance. Glycemic control was improved, and the insulin dosage was decreased to 0.9 U/kg after sodium levothyroxine therapy was initiated *(broken line).* ↑ = Subcutaneous (SC) insulin injection and food.

technique, inappropriate site of injection, a reaction to the cold temperature of insulin stored in the refrigerator, the acidic pH of insulin glargine, or issues with behavior and not an adverse reaction to insulin, per se. Chronic injection of insulin in the same area of the body may cause inflammation and thickening of the skin and subcutaneous tissues and may be caused by an immune reaction to insulin or some other protein (e.g., protamine) in the insulin bottle. Inflammation and thickening of the skin and subcutaneous tissues may impair insulin absorption, resulting in recurrence of clinical signs of diabetes. Rarely, diabetic dogs develop acute focal subcutaneous edema and swelling at the site of an insulin injection. Insulin allergy is suspected in these animals. Treatment includes switching to a less antigenic insulin and to a more purified insulin preparation. Systemic allergic reactions to insulin in dogs have yet to be identified.

Concurrent Disorders Causing Insulin Resistance

Insulin resistance is a condition in which a normal amount of insulin produces a subnormal biologic response. Insulin resistance may result from problems occurring prior to the interaction of insulin with its receptor (e.g., circulating insulin-binding antibodies), at the receptor (e.g., altered insulin receptor binding affinity or concentration), or at steps distal to the interaction of insulin and its receptor (e.g., block in insulin signal transduction). Prereceptor problems reduce free metabolically active insulin concentration and include increased insulin degradation and insulin-binding antibodies. Receptor problems include alterations in insulin-receptor binding affinity and concentration and insulin-receptor antibodies. Postreceptor problems are difficult to differentiate clinically from receptor problems, and both often coexist. In dogs, receptor and postreceptor abnormalities are usually attributable to obesity, circulating acute phase proteins, and inflammatory cytokines (e.g., tumor necrosis factor alpha [TNFα], interleukin-1, interleukin-6) that interfere with insulin signal transduction or a disorder causing excessive or deficient secretion of an insulin-antagonistic hormone, such as cortisol, growth hormone, progesterone, or thyroid hormone (Tilg and Moschen, 2006; Vick et al, 2008).

No insulin dose clearly defines insulin resistance. For most diabetic dogs, control of glycemia can usually be attained using 1.0 U or less of Lente or NPH insulin per kilogram of body weight given twice daily (see Table 6-7). Insulin resistance should be suspected if control of glycemia is poor despite an insulin dosage in excess of 1.5 U/kg, when excessive amounts of insulin (i.e., insulin dosage >1.5 U/kg) are necessary to maintain the blood glucose concentration below 300 mg/dL (Fig. 6-33), and when control of glycemia

TABLE 6-11 **RECOGNIZED CAUSES OF INSULIN INEFFECTIVENESS OR INSULIN RESISTANCE IN DIABETIC DOGS**

CAUSED BY INSULIN THERAPY	DISORDERS TYPICALLY CAUSING SEVERE INSULIN RESISTANCE	DISORDERS TYPICALLY CAUSING MILD OR FLUCTUATING INSULIN RESISTANCE
Inactive insulin	Hyperadrenocorticism	Obesity
Diluted insulin	Diestrus in intact female	Infection
Improper administration technique	Progesterone secreting adrenocortical tumor	Chronic inflammation
Inadequate dose	Diabetogenic drugs	Chronic pancreatitis
Somogyi response	Glucocorticoids	Chronic inflammatory bowel disease
Inadequate frequency of insulin administration	Progestagens	Disease of the oral cavity
Impaired insulin absorption		Chronic kidney disease (CKD)
Insulin-binding antibodies		Hepatobiliary disease
		Cardiac disease
		Hypothyroidism
		Hyperthyroidism
		Pancreatic exocrine Insufficiency
		Hyperlipidemia
		Neoplasia
		Glucagonoma
		Pheochromocytoma

is erratic and insulin requirements are constantly changing in an attempt to maintain control of glycemia. Failure of the blood glucose concentration to decrease below 300 mg/dL (17 mmol/L) during a serial blood glucose curve is suggestive of, but not definitive for, the presence of insulin resistance. An insulin resistance–type blood glucose curve can also result from stress-induced hyperglycemia, the Somogyi response, and other problems with insulin therapy (Table 6-11), and a decrease in the blood glucose concentration below 300 mg/dL can occur with disorders causing relatively mild insulin resistance (e.g., obesity, inflammation). Serum fructosamine concentrations are typically greater than 500 µmol/L in dogs with insulin resistance and can exceed 700 µmol/L if resistance is severe. Unfortunately, an increased serum fructosamine concentration is merely indicative of poor glycemic control not insulin resistance, per se.

The severity of insulin resistance is dependent, in part, on the underlying etiology. Insulin resistance may be mild and easily overcome by increasing the dosage of insulin or may be severe, causing marked hyperglycemia regardless of the type and dosage of insulin administered. Some causes of insulin resistance are readily apparent at the time diabetes is diagnosed, such as obesity and the administration of insulin-antagonistic drugs (e.g., glucocorticoids, progestogens). Other causes of insulin resistance are not readily apparent and require an extensive diagnostic evaluation to be identified. In general, any concurrent inflammatory, infectious, hormonal, neoplastic, or organ system disorder can cause insulin resistance and interfere with the effectiveness of insulin therapy (see Table 6-11). In our experience, the most common concurrent disorders interfering with insulin effectiveness in diabetic dogs include diabetogenic drugs (glucocorticoids), severe obesity, hyperadrenocorticism, diestrus, chronic pancreatitis, CKD, inflammatory bowel disease, oral cavity disease, infections of the urinary tract, hyperlipidemia, and insulin-binding antibodies in dogs receiving beef insulin. Obtaining a complete history and performing a thorough physical examination is the most important initial step in identifying these concurrent disorders. If the history and physical examination are unremarkable, a CBC, serum biochemical analysis, serum cPL, serum progesterone concentration (intact female dog), abdominal ultrasound, and urinalysis with bacterial culture should be obtained to further screen for concurrent illness. Additional tests will be dependent on results of the initial screening tests (Box 6-7).

Treatment and reversibility of insulin resistance is dependent on the etiology. Insulin resistance is reversible with treatable disorders—for example, sodium levothyroxine treatment in a diabetic dog with concurrent hypothyroidism (Ford et al, 1993) or ovariohysterectomy in an intact female diabetic dog in diestrus (see Other Specific Types and Diabetic Remission; Fall et al, 2008b). In contrast, insulin resistance often persists with disorders that are difficult to treat, such as chronic recurring pancreatitis. In some situations, measures can be taken to prevent insulin resistance, such as avoidance of glucocorticoids in diabetic dogs and an ovariohysterectomy at the time diabetes mellitus is diagnosed in an intact female dog.

Insulin Dosage Adjustments

Adjustments in the insulin dosage should always be considered at the time treatment of the insulin-resistant disorder is initiated. How much to decrease the insulin dosage is variable and dependent, in part, on the severity of insulin resistance, the amount of insulin being administered, and the expected rapidity of improvement in insulin resistance after treatment of the disorder. For example, poorly-controlled diabetic dogs with newly diagnosed hypothyroidism will have a rapid improvement in insulin resistance after initiating thyroid hormone treatment (see Fig. 6-33; Ford et al, 1993). Failure to decrease the insulin dosage may result in symptomatic hypoglycemia within days of starting thyroid hormone treatment. In contrast, correction of obesity and subsequent improvement in insulin resistance is a relatively slow

BOX 6-7 Diagnostic Tests to Consider for the Evaluation of Insulin Resistance in Diabetic Dogs

- CBC, serum biochemistry panel, urinalysis
- Bacterial culture of the urine
- Serum cPL (pancreatitis)
- Serum TLI (exocrine pancreatic insufficiency)
- Adrenocortical function tests
  - Urine cortisol-to-creatinine ratio (spontaneous hyperadrenocorticism)
  - Low-dose dexamethasone suppression test (spontaneous hyperadrenocorticism)
  - ACTH stimulation test (iatrogenic hyperadrenocorticism)
- Thyroid function tests
- Baseline serum total and free T_4 (hypothyroidism or hyperthyroidism)
- Endogenous serum TSH (hypothyroidism)
- TSH stimulation test (hypothyroidism)
- Serum progesterone concentration (diestrus in intact female dog)
- Plasma growth hormone or serum IGF-1 concentration (acromegaly)
- Serum insulin antibody test (see Circulating Insulin-Binding Antibodies)
- Fasting serum triglyceride concentration (hyperlipidemia)
- Abdominal ultrasonography (adrenomegaly, adrenal mass, pancreatitis, pancreatic mass)
- Thoracic radiography (cardiomegaly, neoplasia)
- CT or MRI (pituitary mass)

ACTH, Adrenocorticotropic hormone; *CBC,* complete blood count; *cPL,* canine pancreatic-specific lipase; *CT,* computed tomography; *IGF-1,* insulin-like growth factor-1; *MRI,* magnetic resonance imaging; *T_4,* thyroxine; *TLI,* trypsin-like immunoreactivity; *TSH,* thyroid-stimulating hormone (also known as thyrotropin).

process affiliated with a gradual reduction in the insulin dosage over a period of time as obesity improves. Avoiding hypoglycemia is the primary goal when adjusting the insulin dosage. Always err on the side of decreasing the insulin dose too much rather than too little, recognizing that hyperglycemia is not life-threatening but severe hypoglycemia can be. Monitoring urine for ketonuria identifies those dogs in which the reduction in insulin combined with insulin resistance resulted in ketone formation and the need for more insulin (see Chapter 8). When in doubt, I decrease the insulin dose to approximately 0.5 U/kg per injection for diabetic dogs and rely on owner observations regarding the overall health of their pet and the presence of clinical signs suggestive of hypoglycemia. Home blood glucose monitoring and monitoring random urine samples for negative glycosuria may also be considered.

Glucocorticoids and Hyperadrenocorticism

Diabetic dogs are often treated with glucocorticoids for treatment of concurrent disease (e.g., allergic skin disease). Glucocorticoids have the potential to cause severe insulin resistance, creating a tendency for large amounts of insulin to be administered in an attempt to control hyperglycemia (Tiley et al, 2008). If glucocorticoids are required for treatment of a concurrent disease, the glucocorticoid dose should be kept as low as possible and administered as infrequently as possible to minimize the severity of insulin resistance. Insulin dosage requirements will be higher in the presence of insulin resistance to maintain some semblance of glycemic control. It is important to remember the interplay between dosage adjustments of glucocorticoids and the impact of the adjustment on severity of insulin resistance and insulin dosage requirements. Appropriate adjustments in the insulin dose should be done whenever the glucocorticoid dose is increased or decreased to minimize hyper- and hypoglycemia, respectively.

Naturally occurring hyperadrenocorticism and diabetes mellitus are common concurrent diseases in dogs. For most dogs, glycemic control remains poor despite insulin therapy and good glycemic control is generally not possible until the hyperadrenocorticism is controlled. The initial focus should be on treating the hyperadrenal state in a poorly-controlled diabetic dog diagnosed with hyperadrenocorticism. Insulin treatment is indicated; however, aggressive efforts to control hyperglycemia should not be attempted. Rather, a conservative dose (approximately 0.5 U/kg) of intermediate-acting insulin (i.e., Lente or NPH) should be administered twice a day to prevent ketoacidosis and severe hyperglycemia. Monitoring water consumption and frequency of urination is not reliable because both diseases cause polyuria and polydipsia; polyuria and polydipsia may persist if poor control of hyperglycemia persists despite attaining control of hyperadrenocorticism. As control of hyperadrenocorticism is achieved, insulin resistance resolves and tissue sensitivity to insulin improves. Home blood glucose monitoring and testing urine for the presence of glucose can be done by the owner to help prevent hypoglycemia and identify when insulin resistance is resolving. Any blood glucose concentration less than 150 mg/dL (8.4 mmol/L) or urine sample found to be negative for glucose should be followed by a 20% to 25% reduction in the insulin dose and evaluation of control of the hyperadrenocorticism. Critical assessment of glycemic control and adjustments in insulin therapy should be initiated once hyperadrenocorticism is controlled. The ability to establish consistent glycemic control seems more problematic for dogs treated with trilostane versus mitotane (lysodren), presumably because of differences in their mechanism of action and ability to maintain decreased cortisol concentrations (see Chapter 10).

Chronic Pancreatitis

Chronic pancreatitis is the most significant concurrent inflammatory disorder in diabetic dogs. Chronic pancreatitis is identified at necropsy in approximately 35% of diabetic dogs (Alejandro et al, 1988). Most of these animals have a similar history, characterized by poorly controlled diabetes, fluctuating insulin requirements, blood glucose concentrations often greater than 300 mg/dL (17 mmol/L), intermittent lethargy and inappetence, and owner concerns that their pet is "just not doing well." An inability to correct these problems ultimately leads to euthanasia for many dogs. Establishing a diagnosis relies on a combination of clinical signs, physical examination findings, serum cPL, ultrasound evaluation of the pancreas, and clinical suspicion for the disorder (see Pancreatic Enzymes). Feeding a low-fat highly digestible diet is the cornerstone of treatment.

Chronic Kidney Disease

CKD and diabetes mellitus are common geriatric diseases and often occur concurrently. Abnormal kidney function may result from the deleterious effects of the diabetic state (i.e., diabetic nephropathy) or may be an independent problem that has developed in conjunction with diabetes in the geriatric dog. As kidney function declines, human diabetics with concurrent nephropathy are at increased risk for severe hypoglycemia as a result of decreased renal clearance of insulin and decreased renal glucose production by gluconeogenesis (Stumvoll et al, 1997; Rave et al, 2001). Tissue responsiveness to insulin (i.e., insulin sensitivity) is also attenuated, resulting in poorer metabolic control of the diabetic state (Eidemak et al, 1995). Prolonged duration of insulin effect, insulin resistance, and less commonly hypoglycemia are recognized problems in diabetic dogs with concurrent CKD. The interplay between progression and severity of CKD, severity of insulin resistance, and impairment of insulin clearance creates unpredictable

fluctuations in control of glycemia and insulin requirements and frustration for the owner and veterinarian. In addition, reliance on an important indicator of diabetic control (i.e., severity of polyuria and polydipsia) is no longer reliable because of the concurrent CKD. Indicators for possible mild (i.e., non-azotemic) concurrent CKD include persistent polyuria and polydipsia despite good glycemic control of the diabetic state and urine specific gravities less than 1.020 despite 1% to 2% glycosuria. In most cases, treatment for CKD and failure takes priority and insulin therapy is modified, as needed, to attain the best possible control of the diabetic state while trying to avoid hypoglycemia, recognizing that attainment of good control may be difficult and polyuria and polydipsia will persist regardless of the status of glycemic control.

Hypertriglyceridemia

Increased serum concentrations of cholesterol and triglycerides are common in newly diagnosed diabetic dogs and usually resolve after initiation of insulin treatment (see Serum Cholesterol and Triglyceride Concentrations). Persistent hypertriglyceridemia may impair insulin receptor-binding affinity, promote downregulation of insulin receptors, and cause a postreceptor defect in insulin action (Berlinger et al, 1984; Bieger et al, 1984) Hypertriglyceridemia may be secondary to other disorders or may be a primary hyperlipidemic disorder (Box 6-8). The insulin resistance caused by hypertriglyceridemia is most commonly appreciated in diabetic dogs that develop hypothyroidism and in diabetic Miniature Schnauzers with idiopathic hyperlipidemia but should be considered in any poorly-controlled diabetic dog with persistent lipemia (Xenoulis et al, 2011). Unfortunately, hypertriglyceridemia is common in poorly-regulated diabetic dogs, and the differentiation between hypertriglyceridemia caused by poorly controlled diabetes versus hypertriglyceridemia that has developed independent of the diabetic state can be difficult. As a general rule, serum triglyceride concentrations in poorly-controlled diabetics are usually less than 500 mg/dL. Serum triglyceride concentrations in excess of 500 mg/dL, especially 800 mg/dL, should raise suspicion for a concurrent disorder causing the hypertriglyceridemia, most notably pancreatitis, hypothyroidism, and primary hyperlipidemic disorders. Restriction of dietary fat is the cornerstone of therapy for hypertriglyceridemia.

BOX 6-8 Causes of Hyperlipidemia in Dogs and Cats

- Postprandial hyperlipidemia
- Primary hyperlipidemia
  - Idiopathic hyperlipoproteinemia (Miniature Schnauzers)
  - Idiopathic hyperchylomicronemia (cats)
  - Lipoprotein lipase deficiency (cats)
  - Idiopathic hypercholesterolemia
- Secondary hyperlipidemia
  - Hypothyroidism
  - Diabetes mellitus
  - Hyperadrenocorticism
  - Pancreatitis
  - Cholestasis
  - Hepatic insufficiency
  - Nephrotic syndrome
  - Drug-induced hyperlipidemia
    - Glucocorticoids
    - Progestagens (cats)

CHRONIC COMPLICATIONS OF DIABETES MELLITUS

Complications resulting from diabetes, its treatment, or affiliated disorders are common in diabetic dogs and include blindness and anterior uveitis resulting from cataract formation, diabetic retinopathy (retinal hemorrhage, microaneurysms), hypoglycemia, chronic pancreatitis, recurring infections, poor glycemic control, and ketoacidosis (see Table 6-4). Many owners are hesitant to treat their newly diagnosed diabetic dog because of knowledge regarding chronic complications experienced in human diabetics and concern that a similar fate awaits their pet. However, clients should be assured that the devastating chronic complications of human diabetes (e.g., nephropathy, neuropathy, vasculopathy) require years to develop and become clinical and therefore are uncommon in diabetic dogs. Diabetes mellitus is a disease of older dogs and most do not live beyond 5 years from the time of diagnosis (Fall et al, 2007). In our experience, owners are usually willing to "tackle" the care of their diabetic dog once the fears related to chronic complications seen in human diabetics are alleviated and assurances are made that administering insulin is easy and dogs are very tolerant of insulin injections.

Chronic hyperglycemia is the central initiating factor for all types of microvascular complications in diabetic humans. The duration and severity of hyperglycemia is strongly correlated with the extent and progression of diabetic microvascular disease. Although all cells are exposed to hyperglycemia, hyperglycemic damage is limited to those cell types (e.g., endothelial cells in the retina, glomerulus, and nerve vasa nervosum) that develop intracellular hyperglycemia (Brownlee et al, 2011). The common pathophysiologic feature of diabetic microvascular disease is progressive narrowing and eventual occlusion of vascular lumina, which results in inadequate perfusion and function of affected tissues and microvascular cell loss.

Four major hypotheses for how hyperglycemia causes diabetic complications have been extensively studied and are listed here: (1) increased polyol pathway flux involving aldose reductase and sorbitol, (2) increased intracellular formation of advanced glycation end products, (3) activation of protein kinase C, and (4) increased hexosamine pathway flux with increased shunting of glucose into the hexosamine pathway (Brownlee et al, 2011). All four of these different pathogenic mechanisms reflect a single hyperglycemia-induced process: overproduction of superoxide by the mitochondrial electron transport chain. Hyperglycemia increases the production of reactive oxygen species, which inhibits the activity of a key glycolytic enzyme (glyceraldehyde-3-phosphate dehydrogenase). Inhibition of this enzyme results in the upstream accumulation of glycolytic intermediates which, in turn, activate each of the four proposed mechanisms. The pathophysiologic mechanisms for chronic complications in diabetic dogs have been poorly characterized but are assumed to be comparable to those in diabetic humans.

Cataracts

Cataract formation is the most common long-term complication of diabetes mellitus in the dog (see Fig. 6-4). A retrospective-cohort study on the development of cataracts in 132 diabetic dogs referred to a university referral hospital found cataract formation in 14% of dogs at the time diabetes was diagnosed and a time interval for 25%, 50%, 75%, and 80% of the study population to develop cataracts at 60, 170, 370, and 470 days, respectively (Beam et al, 1999). The pathogenesis of diabetic cataract formation is thought to be related to altered osmotic relationships in

the lens induced by the accumulation of sorbitol and galactitol, which are sugar alcohols that are produced following reduction of glucose and galactose by the enzyme aldose reductase in the lens. Sorbitol and galactitol are potent hydrophilic agents and cause an influx of water into the lens, leading to swelling and rupture of the lens fibers and the development of cataracts (Richter et al, 2002). Cataract formation is an irreversible process once it begins, and it can occur quite rapidly. Diabetic dogs that are poorly controlled and have problems with wide fluctuations in the blood glucose concentration seem especially at risk for rapid development of cataracts. Good glycemic control and minimal fluctuation in the blood glucose concentration prolongs the onset of cataract formation. Once blindness occurs as a result of cataract formation, the need for stringent blood glucose control is reduced.

Blindness may be eliminated by removing the abnormal lens. Vision is restored in approximately 80% of diabetic dogs that undergo cataract removal (Appel et al, 2006; Sigle and Nasisse, 2006). Factors that affect the success of surgery include the degree of glycemic control preceding surgery, presence of retinal disease, and presence of lens-induced uveitis. Acquired retinal degeneration affecting vision is more of a concern in older diabetic dogs than is diabetic retinopathy. Fortunately, acquired retinal degeneration is unlikely in an older diabetic dog with vision immediately before cataract formation. If available, electroretinography should be performed before surgery to evaluate retinal function.

In a study by Kador, et al., (2010), the topical administration of the aldose reductase inhibitor Kinostat significantly delayed the onset and/or progression of cataracts in dogs with diabetes mellitus during a 12-month period. If Kinostat becomes available commercially, it may offer a medical option for preventing or slowing the formation of cataracts in diabetic dogs.

Lens-Induced Uveitis

During embryogenesis, the lens is formed within its own capsule and its structural proteins are not exposed to the immune system. Therefore, immune tolerance to the crystalline proteins does not develop (van der Woerdt et al, 1992). During cataract formation and reabsorption, lens proteins are exposed to local ocular immune system, resulting in inflammation and uveitis. Uveitis that occurs in association with a reabsorbing, hypermature cataract may decrease the success of cataract surgery and must be controlled before surgery (Bagley and Lavach, 1994). The treatment of lens-induced uveitis focuses on decreasing the inflammation and preventing further intraocular damage. Topical ophthalmic glucocorticoids (e.g., prednisone acetate) are the most commonly used drugs for the control of ocular inflammation. However, systemic absorption of topically applied glucocorticoids may cause insulin resistance and interfere with glycemic control of the diabetic state, especially in toy and miniature breeds. An alternative is the topical administration of nonsteroidal anti-inflammatory agents, such as diclofenac (Voltaren) or flurbiprofen ophthalmic (Ocufen). Although not as potent an anti-inflammatory agent as glucocorticoids, nonsteroidal anti-inflammatory drugs should not interfere with glycemic control.

Corneal Ulceration

Diabetes mellitus has been associated with pathologic changes in the corneas of dogs, which are directly related to the degree of diabetic control (Yee et al, 1985), and a significant reduction in corneal sensitivity in all regions of the cornea has been documented in diabetic dogs, compared with non-diabetic normoglycemic dogs (Good et al, 2003). Corneal nerves are critical for eliciting and regulating corneal protection via their role in the mediation of tear production and eyelid closure and regulation of corneal collagen expression and epithelial cell function and integrity (Baker et al, 1993; Marfurt, 2000). Corneal sensory deficits are thought to be a component of the diffuse neuropathy affecting the peripheral sensorimotor nervous system of diabetic humans and animals and may have important implications regarding corneal healing and the development of recurrent or nonhealing corneal ulcers in diabetic dogs.

Diabetic Retinopathy

Diabetic retinopathy in the dog is characterized histologically by damage to the retinal vasculature and retinal neurons, specifically degeneration of retinal ganglion cells (Howell et al, 2013). Ophthalmoscopically identifiable retinal hemorrhages and microaneurysms are considered the maker for diabetic retinopathy in dogs. Additional ophthalmoscopic findings include dilatation and tortuosity of retinal venules, hyper-reflectivity of the tapetal portion of the retina, and chorioretinal exudates. In one study, 11 of 52 (21%) diabetic dogs developed ophthalmoscopic signs of retinal hemorrhages or microaneurysms, compared with 1 of 17 (0.6%) non-diabetic dogs (Landry et al, 2004). Median time from diagnosis of diabetes to diagnosis of retinopathy was 1.4 years (range, 0.5 to 3.2 years). Histologic changes include an increased thickness of the capillary basement membrane, loss of pericytes, capillary shunts, and microaneurysms. The cause of diabetic retinopathy is probably multifactorial and may involve biochemical changes secondary to hyperglycemia and increased aldose reductase activity, advanced glycation end products, hemodynamic alterations, and vascular endothelial and pericyte loss (Merimee, 1990; Stitt, 2003). Risk factors for development of diabetic retinopathy have been poorly characterized in diabetic dogs, although status of glycemic control may be associated with progression of diabetic retinopathy (Engerman and Kern, 1987). Retinal ganglion cell degeneration is significantly inhibited by good to moderate glycemic control in diabetic dogs (Howell et al, 2013). Loss of vision is uncommon in dogs with diabetic retinopathy.

Unfortunately, the rapid development of cataracts often inhibits the ability to evaluate the retina in the dog with diabetes mellitus. Because of the high incidence of cataract formation, the retinas should always be evaluated in the newly-diagnosed diabetic pet to ensure normal function and lack of grossly visible disease should cataract formation and subsequent lens removal become necessary in the future. Lens removal would be unwarranted in a diabetic dog with retinal changes sufficiently severe to result in blindness itself. An electroretinogram can also be used to evaluate the function of the retina prior to cataract surgery.

Diabetic Neuropathy

Although a common complication in diabetic cats, diabetic neuropathy is infrequently recognized in the diabetic dog (Braund and Steiss, 1982; Johnson et al, 1983; Katherman and Braund, 1983; Morgan et al, 2008). Diabetic neuropathy in the dog is primarily a distal polyneuropathy, characterized by segmental demyelination and remyelination and axonal degeneration. Subclinical neuropathy is more common than severe neuropathy resulting in clinical signs. Clinical signs consistent with diabetic neuropathy are most commonly recognized in dogs that have been diabetic for a long period of time (i.e., 5 years or longer), although dogs have been diagnosed with diabetic neuropathy shortly after the diagnosis of

diabetes is established (Morgan et al, 2008). Clinical signs and physical examination findings suggestive of diabetic neuropathy include pelvic limb paresis, abnormal gait, decreased muscle tone, muscle atrophy, depressed limb reflexes, and deficits in postural reaction testing. Electrodiagnostic abnormalities include spontaneous sharp waves and fibrillation potentials and decreased M-wave amplitude on electromyogram, suggestive of axonal disease, and decreased motor and sensory nerve conduction velocities, suggestive of demyelinating disease (Steiss et al, 1981; Boulton et al, 2005; Morgan et al, 2008). There is no specific treatment for diabetic neuropathy besides meticulous metabolic control of the diabetic state. See Chapter 7 for more information on diabetic neuropathy.

Diabetic Nephropathy

Diabetic nephropathy has occasionally been reported in the dog. Diabetic nephropathy is a microvascular disease involving the capillary and precapillary arterioles and is manifested mainly by thickening of the capillary basement membrane. Histopathologic findings include membranous glomerulonephropathy, glomerular and tubular basement membrane thickening, an increase in the mesangial matrix material, the presence of subendothelial deposits, glomerular fibrosis, and glomerulosclerosis (Steffes et al, 1982; Jeraj et al, 1984). Glucose plays a central role in the development of microvascular damage. Clinical signs depend on the severity of glomerulosclerosis and the functional ability of the kidney to excrete metabolic wastes. Initially, diabetic nephropathy is manifested as proteinuria, primarily albuminuria. As glomerular changes progress, glomerular filtration becomes progressively impaired, resulting in the development of azotemia and eventually uremia. With severe fibrosis of the glomeruli, oliguric and anuric kidney failure develop.

Monitoring urine for the presence of microalbuminuria is used as an early marker for development of diabetic nephropathy in diabetic humans. Microalbuminuria occurs in diabetic dogs and increased urine albumin-to-creatine ratios precede increased urine protein-to-creatinine ratios. In one study, 11 (55%) of 20 diabetic dogs had an increase in the urine albumin-to-creatinine ratio and only 6 of these 11 dogs also had an increase in urine protein-to-creatinine ratio, suggesting that monitoring urine albumin-to-creatinine ratio may be of value as an early marker for kidney disease in diabetic dogs (Mazzi et al, 2008). However, the predictive value of microalbuminuria for diabetic nephropathy and the clinical relevance of microalbuminuria in diabetic dogs remains to be clarified. Diabetic nephropathy is a significant chronic complication in diabetic humans that takes years to progress to chronic end-stage kidney disease; a time line that may explain why clinically relevant diabetic nephropathy is uncommon in diabetic dogs. Presumably in most dogs, diabetes mellitus and CKD develop as independent events in aged dogs.

Regardless, proteinuria, kidney function, and systemic blood pressure should be monitored in diabetic dogs that have developed microalbuminuria. There is no specific treatment for diabetic nephropathy apart from meticulous metabolic control of the diabetic state, conservative medical management of the kidney disease, administration of angiotensin converting enzyme (ACE) inhibitors to minimize proteinuria, and control of systemic hypertension.

Systemic Hypertension

Diabetes mellitus and hypertension commonly coexist in dogs. Struble et al. (1998) found the prevalence of hypertension to be 46% in 50 insulin-treated diabetic dogs, in which hypertension was defined as systolic, diastolic, or mean blood pressure greater than 160, 100, and 120 mm Hg, respectively. Median (range) systolic, diastolic, and mean blood pressure in the hypertensive diabetic dogs were 175 (160 to 205) mmHg, 112 (101 to 150) mmHg, and 132 (120 to 186) mmHg, respectively. The development of hypertension was associated with the duration of diabetes and an increased albumin-to-creatinine ratio in the urine. Diastolic and mean blood pressure were higher in dogs with longer duration of disease. A correlation between control of glycemia and blood pressure was not identified. Systemic hypertension may result from existing subclinical kidney disease or develop secondary to the effects of diabetes on vascular compliance, glomerular function, or some other mechanism (Dukes, 1992). Treatment for hypertension should be initiated if the systolic blood pressure is consistently greater than 160 mm Hg.

PROGNOSIS

The prognosis for dogs diagnosed with diabetes mellitus depends, in part, on owner commitment to treating the disorder, ease of glycemic regulation, presence and reversibility of concurrent disorders, avoidance of chronic complications associated with the diabetic state, and minimization of the impact of treatment on the quality of life of the owner (see Table 6-5). In a large study involving insured dogs in Sweden, the median survival time after the first diabetes mellitus claim (686 dogs) was 57 days and for dogs surviving at least 1 day (463 dogs) was 2.0 years (Fall et al, 2007). For dogs surviving at least 30 days after the first diabetes mellitus claim (347 dogs), the proportion of dogs surviving 1, 2, and 3 years was 40%, 36%, and 33%, respectively. However, survival times vary between countries and between socioeconomic regions within a country, and survival time is somewhat skewed because dogs are often 8 to 12 years old at the time of diagnosis; a relatively high mortality rate exists during the first 6 months because of concurrent life-threatening or uncontrollable disease (e.g., ketoacidosis, acute pancreatitis, kidney failure). In our experience, diabetic dogs that survive the first 6 months can easily maintain a good quality of life for longer than 5 years with proper care by the owners, timely evaluations by the veterinarian, and good client-veterinarian communication.

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