CHAPTER 7

Feline Diabetes Mellitus

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CHAPTER CONTENTS

Diabetes mellitus in dogs and cats differs in a number of ways, which are important to consider for work-up and therapy. The majority of cats suffer a type of diabetes similar to type 2 in humans; in dogs, this type is extremely rare or may not exist at all. Unlike dogs, obesity is an important risk factor for the development of diabetes in cats; the difference is most likely associated with the different types of diabetes in the two species, because obesity and type 2 diabetes are closely related. A substantial percentage of cats with type 2 diabetes experience diabetic remission, and achievement of remission is nowadays one of the major treatment goals in diabetic cats. In dogs, however, remission is a very rare event, it usually only occurs after castration of a bitch with diestrus-associated diabetes. In cats, other endocrine disorders (e.g., hypersomatotropism and hyperadrenocorticism) are associated with the development of diabetes in most cases, whereas concurrent diabetes is relatively rare in dogs with hyperadrenocorticism and variable in the case of hypersomatotropism. Cats are prone to stress hyperglycemia, which may cause difficulties in diagnosis and monitoring of the disease, whereas in dogs, stress associated increase in blood glucose is of minor importance. The so-called renal threshold for glucose absorption is higher in cats than in dogs, rendering measurement of urine glucose for monitoring purposes in diabetic cats even more problematic than in the dog. Diabetes-associated complications differ between the two species: diabetic cataract is rare in cats and common in dogs, whereas gait abnormalities due to diabetic neuropathy are common in cats and rare in dogs. Of note, both cataract and diabetic neuropathy also exist in the respective counterpart, however, usually at a subclinical level. Cats, but not dogs are obligate carnivores and therefore, dietary management is different. Last but not least, duration of effect of exogenous insulin in cats is often shorter than in dogs.

PREVALENCE AND RISK FACTORS IN HUMANS AND CATS

In humans, diabetes mellitus is one of the most common chronic diseases in nearly all countries (Whiting et al, 2011). Type 2 diabetes is the predominant form, which accounts for approximately 90% of cases worldwide. Type 2 has long been the disease of elderly people; however, this has changed substantially and nowadays more and more children and young adults are affected. Due to the dramatic increases in prevalence during the last few decades, diabetes has also been called a "new epidemic" (Kaufman, 2002). The International Diabetes Federation routinely publishes estimates of diabetes prevalence every 3 years starting in the year 2000. In 2011, there were 366 million people with diabetes, and the number is expected to rise to 552 million by 2030. Although the number differs between countries, every region of the world will have an increase well in excess of adult population growth (Whiting et al, 2011). Excessive caloric intake leading to obesity and sedentary lifestyle are known to be the major risk factors in humans; an increase in the incidence of obesity has always been paralleled by an increase in diabetes incidence. Aging, female sex, and belonging to certain racial and ethnic groups are additional critical factors. There is no doubt that diabetes has become one of the most important global health problems (Kaufman, 2002; Buse et al, 2011; Whiting et al, 2011).

As in humans, diabetes is a common disorder in cats. Different from human medicine, however, there are only limited data on the prevalence of the disease. Some recent publications provide a general overview of the current situation, although the methods of data collection differ. Most numbers reflect the proportion of diabetic cats in a particular practice or a hospital ("hospital prevalence") and not the situation in the field. A study from the United States reported an increase in hospital prevalence over 30 years from 0.08% in 1970 to 1.2% in 1999. At the same time, case fatality at the first visit decreased from 40% to 10% suggesting either improvement in treatment regimens or an increased willingness of owners to undertake long-term management (Prahl et al, 2007). Studies from Australia showed overall hospital prevalence (i.e., all cat breeds) of 0.55% and 0.74%; prevalence in the Burmese cats was much higher with 1.8% and 2.2%, respectively (Baral et al, 2003; Lederer et al, 2009). Recently, a non-hospital prevalence was evaluated in a large population of insured cats in the United Kingdom and was found to be 0.43%. Prevalence of diabetes in the Burmese cats was again higher with 1.8%, which compared well with the studies from Australia (McCann et al, 2007). As in humans, obesity is a major risk factor for diabetes in cats, and overweight cats are several times more likely to develop diabetes than optimal weight cats (Scarlet and Donoghue, 1998). Physical inactivity and indoor confinement, which is most likely associated with obesity ("sedentary lifestyle") as well as advancing age, have also been identified as important risk factors in cats. The overrepresentation of male cats within the feline diabetic population has been known for a long time and has been confirmed by various studies (Panciera et al, 1990; Crenshaw and Peterson, 1996; McCann et al, 2007; Prahl et al, 2007; Slingerland et al, 2009). The exception is the Burmese cat, for which a gender predisposition is less clear. A study performed in the United Kingdom did not identify male gender as a risk factor in the Burmese breed, whereas in the study from Australia, male Burmese cats were twice as likely to develop diabetes as were female Burmese cats (McCann et al, 2007; Lederer et al, 2009). The reason for the male predominance in most breeds has not yet been clarified. What is known is that insulin sensitivity is generally lower in normal male than in normal female cats and that cats with reduced insulin sensitivity have a higher risk of becoming glucose intolerant after weight gain. Male cats tend to gain more weight when fed ad libitum than female cats (Appleton et al, 2001). It is not clear if neutering is an independent risk factor, as one study found neutering (in both sexes) to be associated with an increased risk of diabetes, whereas another study did not find this association (McCann et al, 2007; Prahl et al, 2007). Neutered cats are at greater risk of gaining weight, and it is probably the increased risk of obesity that contributes to the development of diabetes (McCann et al, 2007). In the United States, no particular breed of cats appears to be associated with an increased risk for diabetes; in Australia, New Zealand, and the United Kingdom, however, the Burmese breed is known to be at increased risk (Panciera et al, 1990; Crenshaw and Peterson, 1996; Rand et al, 1997; Wade et al, 1999; McCann et al, 2007; Lederer et al, 2009). In a study using a large insured cat population in the United Kingdom, Burmese cats were approximately four times more likely to develop diabetes than non-pedigree cats. Data from New Zealand point to a genetic predisposition; the differences between the countries are most likely the result of different breeding programs and different lines within the Burmese breed (Wade et al, 1999; McCann, et al, 2007). Treatment with glucocorticoids or progestagens also increases the likelihood of the development of diabetes (Slingerland et al, 2009). In summary, many of the risk factors for development of diabetes are similar in humans and cats, including obesity, physical inactivity, and increasing age. Interestingly, however, the predominance in the male gender is unique to the cat. Although data are scarce, it is the impression of most endocrinologists that the incidence of diabetes in cats is increasing, which is most likely associated with the increased incidence of obesity, physical inactivity, and longevity.

CLASSIFICATION OF DIABETES MELLITUS

Traditionally, the classification of diabetes mellitus in cats has more or less followed the scheme used in human medicine. Although the etiopathogenic mechanisms may not be completely identical, the "human model" provides a guide for identification and differentiation of the various forms of the disease.

The first real attempt to classify human diabetes in a uniform way was done in 1965 by the World Health Organization (WHO) Expert Committee, recognizing that without a clear classification, it is difficult to take a systematic epidemiological approach to clinical research and develop evidence-based guidelines for therapy and prevention (George et al, 2011). At that time, little was known about the etiology of diabetes and the classification scheme contained somewhat confusing categories. The second report of the WHO Expert Committee in 1980 offered a classification that was widely accepted. Two main classes were introduced: insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). Additional classes were other types and gestational diabetes mellitus. During the following years, understanding of the complex facets of the diabetic disease improved, leading to a new classification scheme that included both etiology and clinical stages. The categories were named type 1, type 2, other specific types, and gestational diabetes. It was suggested that the terms *insulin-dependent* and *non-insulin-dependent diabetes mellitus (IDDM, NIDDM)* should be abandoned, because they were considered confusing and frequently resulted in patients being classified on the basis of treatment rather than on etiopathogenesis (World Health Organization, 1999). Up until now, a few updates were made; however, there are no fundamental changes compared with the report in 1999 (George et al, 2011; American

Diabetes Association, 2013). Although the scheme is helpful, it is recognized that assigning a type of diabetes to an individual often depends on the circumstances present at the time of diagnosis, and individuals may not easily fit into one class. For instance, a person who becomes diabetic after receiving exogenous steroids may regain normoglycemia after the discontinuation of the drug, but may again develop diabetes after episodes of pancreatitis.

BOX 7-1 Etiological Classification of Diabetes Mellitus in Humans

I. Type 1 diabetes
(β-cell destruction, usually leading to absolute insulin deficiency)
  a. Immune-mediated
  b. Idiopathic
II. Type 2 diabetes
(ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance)
III. Other specific types of diabetes
  a. Genetic defects of β-cell function
  b. Genetic defects in insulin action
  c. Diseases of the exocrine pancreas
  (e.g., pancreatitis, neoplasia, trauma, pancreatectomy)
  d. Endocrinopathies
  (e.g., hypersomatotropism, hyperadrenocorticism, pheochromocytoma, hyperthyroidism, hyperaldosteronism)
  e. Drug- or chemical-induced
  f. Infection
  g. Uncommon forms of immune-mediated diabetes
  h. Other genetic syndromes sometimes associated with diabetes
IV. Gestational diabetes mellitus

Modified from American Diabetes Association: Diagnosis and classification of diabetes mellitus, *Diabetes Care* 36 (suppl 1):67, 2013.

Similarly, a woman with gestational diabetes may continue to be diabetic after delivery and may in fact suffer from type 2 diabetes (American Diabetes Association, 2013). Box 7-1 lists the classification scheme according to etiology currently used in human medicine. Fig. 7-1 displays the clinical stages and their dynamics within the four types of diabetes.

Types of Diabetes in Humans

The discussion of the various types of diabetes is done separately for humans and cats; this will enable a better overview over the current state of knowledge in the two species. Many of the findings in humans may also be of importance for feline diabetes, and it is recommended to read the sections on humans prior to reading the feline sections.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus accounts for 5% to 10% of human cases and was previously known as IDDM or juvenile-onset diabetes. Although it is commonly seen in childhood and adolescence, it can occur at any age, even in the 8th or 9th decade of life. It most commonly (> 90%) results from cellular-mediated autoimmune destruction of the β-cells leading to failure of insulin synthesis (American Diabetes Association, 2013). The characteristic pathological lesion in the pancreas is the presence of mononuclear immune cells around and within the islets. This infiltration, also called *insulitis,* is dominated by T lymphocytes, in particular "cytotoxic" (cluster of differentiation 8 [CD8]) T lymphocytes; others are "helper" (cluster of differentiation 4 [CD4]) T lymphocytes and macrophages. The destructive process is limited to the β-cells, all other endocrine cells of the islets are spared (Peakman, 2011). The rate of β-cell destruction is variable; rapid destruction is often seen in children, whereas the destructive process often is prolonged in adults (American Diabetes Association, 2013). Interestingly, the pattern of β-cell destruction is markedly heterogenous, and an intact pancreatic islet can be located next to an

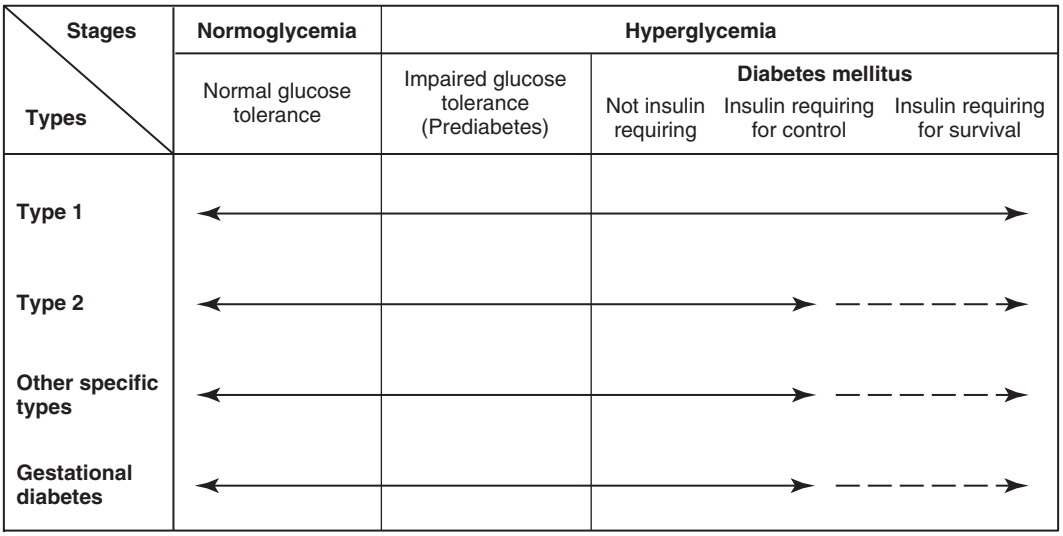

FIGURE 7-1 Clinical stages and etiological types of diabetes in humans. *Arrows* indicate that an individual may move between the clinical stages; *broken arrows* illustrate that individuals in one category who would by definition not require insulin for survival may develop the need for insulin under certain circumstances (e.g., disease progression, development of diabetic ketoacidosis [DKA]). (Modified from George K, et al.: Classification and diagnosis of diabetes mellitus. In Wass JAH, Stewart PM, Amiel SA, Davies MC, editors: *Oxford textbook of endocrinology and diabetes,* ed 2, Oxford, 2011, Oxford University Press; and American Diabetes Association: Diagnosis and classification of diabetes mellitus, *Diabetes Care* 36[suppl 1]:67, 2013.)

islet with completely destroyed β-cells (Klinke, 2008). Recently, the widely-held belief that the disease only becomes clinically apparent when 80% to 90% of the individual's β-cells are destroyed has been challenged. It was suggested, that the extent of β-cell destruction at which hyperglycemia develops is age-dependent. In younger humans (at age 20) a reduction of 40% of β-cell mass was sufficient to precipitate clinical signs (Klinke, 2008). A major marker of autoimmune type 1 diabetes is the presence of circulating autoantibodies against glutamic acid decarboxylase 65 (GAD65), islet antigen-2 (IA-2), insulin, and zinc transporter 8 (ZnT8). One or more of these islet-related autoantibodies can be detected months to years before the clinical onset of the disease in most human patients. Their measurement is useful to differentiate type 1 diabetes from other types in newly diagnosed individuals and to follow individuals at risk to predict the development of the disease. Although their predictive value is very high, not all subjects with autoantibodies will develop diabetes, most likely because of protective genes. With time, autoantibodies tend to decline (Delli et al, 2010; Masharani and German, 2011). What exactly triggers the autoimmune process has not yet been unraveled. It has been known for quite some time that genetic factors increase the predisposition for the disease and that genetic susceptibility is most closely associated with allelic variants within the human leukocyte antigen (HLA) region that lie on the short arm of chromosome 6. High and lower risk haplotypes as well as protective haplotypes have been identified. Genes outside of the HLA region also contribute to the risk of type 1 diabetes, however, to a much smaller extent (Erlich et al, 2008; Concannon et al, 2009). Although genetics play an important role, studies in monozygotic twins revealed that the concordance rate is only approximately 50%, indicating that other causes are at least as important. Environmental factors, assumed to be associated with increased risk of type 1 diabetes, are virus infections (e.g., mumps virus, rubella virus, and the Cocksackie B virus), dietary factors (short breast-feeding/bovine milk), and toxic substances. The incidence of type 1 diabetes increases steadily, in particular in Western societies. It has been suggested that the sharp rise is due to a change in environmental factors operating early in life. According to the "hygiene hypothesis," the lack of exposure to common pathogens (in particular parasites) in a clean, more sterile environment may result in an exaggerated immune response (Bilous and Donelly, 2010; Masharani and German, 2011).

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus was previously referred to as NIDDM or adult-onset diabetes and accounts for up to 90% of human cases (American Diabetes Association, 2013). Type 2 diabetes is a complex and heterogeneous disease resulting from a large number of genetic and environmental insults. The genetic association is stronger than for type 1 diabetes, and the concordance rate in monozygotic twins is much higher. Depending on the population studied, the latter may be as high as 90%; however, it has been assumed that part of the high rate may also be due to similar environmental factors (Bilous and Donnelly, 2010; Masharani and German, 2011).

Type 2 diabetes is characterized by two defects, namely insulin resistance and relative insulin deficiency due to β-cell dysfunction (as opposed to absolute deficiency in type 1 diabetes) (American Diabetes Association, 2013) (Fig. 7-2). It has long been assumed that insulin resistance was the primary and most important defect. However, most humans with insulin resistance do not develop diabetes, because their β-cells are able to compensate by augmenting insulin production and secretion. It is now generally agreed that individuals cannot develop type 2 diabetes without having dysfunctional β-cells. Therefore, at the time of diagnosis, both insulin resistance and β-cells abnormalities are present (Robertson, 2009; Masharani and German, 2011). The term *insulin resistance* describes the inability of insulin to exert its normal biological effects at concentrations that are effective in normal individuals. The main sites of insulin resistance are liver, muscle, and adipose tissue. The defects seem to involve the insulin receptor binding only to a minor extent; most abnormalities are at post-receptor levels in the insulin-signaling cascade. Insulin resistance leads to impaired suppression of hepatic gluconeogenesis (under basal conditions as well as after meals) and impaired glucose uptake of peripheral tissues (Yki-Järvinen, 2010). A large number of genes associated with the disease have been identified, the majority of which are associated with reduction in β-cell function; only a few are related to insulin sensitivity (De Silva and Frayling, 2010; Schäfer et al, 2011; Kahn et al, 2012). Besides genetics, insulin sensitivity is negatively influenced by various factors, including obesity, physical inactivity, some drugs, and high glucose levels. Obesity is recognized as the major critical factor worldwide. With an increase in obesity, there has been a parallel global increase in the incidence of type 2 diabetes mellitus. Approximately 80% of humans with type 2 diabetes are obese, and the risk of diabetes increases with body fat mass. The pattern of obesity is important, as central (intra-abdominal) fat carries a much higher risk than fat deposition at other sites. Individuals with type 2 diabetes with a body mass index not meeting the definition for obesity may still have an excessive

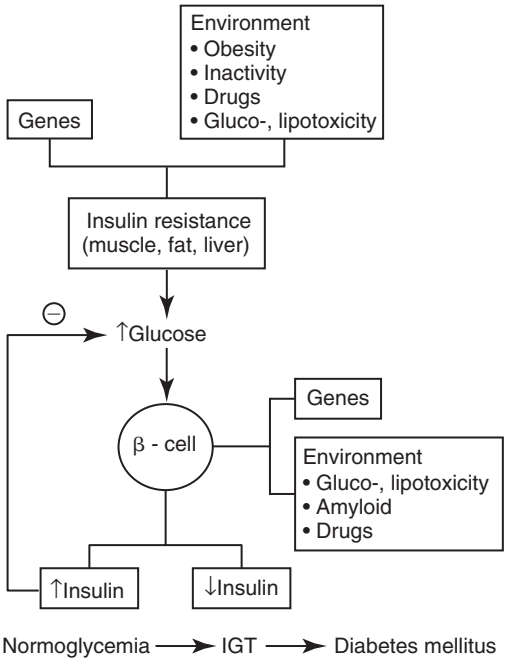

FIGURE 7-2 Simplified model of etiopathogenesis of type 2 diabetes mellitus. Although this graph is taken from human medicine, it is currently assumed that the principal factors are similar in cats. At the time of diagnosis of type 2 diabetes the two defects, insulin resistance and β-cell dysfunction, are present. Initially, β-cells are able to compensate for insulin resistance by increasing insulin synthesis and normoglycemia is maintained. With time, however, dysfunctional β-cells are not able to meet the increased demand, leading to impaired glucose tolerance and thereafter, to overt diabetes. In individuals without β-cell defect, diabetes mellitus will not develop because β-cells are able to compensate. (Modified from Bilous R, Donnelly R: *Handbook of diabetes,* ed 4, 2010, Wiley-Blackwell.) *IGT,* Impaired glucose tolerance.

intra-abdominal fat accumulation (Bilous and Donnelly, 2010). The discovery that adipose tissue (in particular the central visceral stores) is an active endocrine organ, and part of the innate immune system has sparked intense research on obesity. Factors secreted by adipose tissue play a major role in the regulation of metabolism. These factors include non-esterified fatty acids (NEFAs) and proteins, called *adipocytokines,* which act in an autocrine, paracrine, or endocrine fashion. Adipose tissue in lean subjects secretes relatively high levels of the adipocytokine adiponectin, which has anti-inflammatory actions and is associated with an increase in insulin sensitivity and therefore with a favorable metabolic status. With obesity, adiponectin secretion decreases considerably and instead, large amounts of NEFA, leptin, and pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1) and others, are secreted by adipocytes and/or activated macrophages within the adipose tissue. These factors impair insulin signaling and therefore induce or worsen insulin resistance. Additionally, inflammatory factors are released into the systemic circulation and may promote inflammation in other tissues, including the islets (Rasouli and Kern, 2008; Donath and Shoelson, 2011).

Dysfunction of β-cells is crucial in the development of type 2 diabetes mellitus. Initially, the β-cells are able to increase insulin synthesis and release to meet the increased demand caused by the insulin resistance. With time, however, β-cells start to fail, first leading to glucose intolerance, which is usually followed by overt diabetes mellitus. It is currently assumed that the primary defect is a genetic predisposition and that additional acquired or environmental factors amplify the genetic damage, ultimately worsening the hyperglycemia (Robertson, 2009). By the time of diagnosis, β-cell function is reduced by approximately 50% and continues to decline. Beta-cell mass will also decrease during type 2 diabetes, however, not to an extent that would fully explain the extent of dysfunction. Therefore, besides morphological defects (reduction in number of β-cells), important functional defects contribute to the disease. The latter may be, at least in part, reversible and are therefore an interesting topic for new drug therapies (Robertson, 2009). Characteristic reflections of β-cell defects include disruption of the normal basal oscillatory pattern of insulin release, reduced or absent first phase insulin secretion in response to intravenous (IV) glucose (and with time reduced second phase release), reduced insulin response to a mixed-meal, and insufficient conversion of proinsulin to insulin. The other cells of the islets remain intact (Alsahli and Gerich, 2010). Type 2 is a polygenic disease, and many genetic variants contribute to the susceptibility of the disease. As already mentioned, most of the risk genes affect β-cell function, in particular glucose-stimulated insulin secretion, incretin-stimulated insulin secretion, and proinsulin-to-insulin conversion. So far, the most important type 2 risk gene is the gene encoding transcription factor 7-like 2 (TCF7L2); mutations are mainly associated with an impairment of the incretin effect (Schäfer et al, 2011) (incretins are discussed in Oral Hypoglycemic Agents and Non-Insulin Injectables). Acquired or environmental factors that worsen the damage of the β-cells in genetically predisposed individuals include glucotoxicity, lipotoxicity, oxidative stress, pro-inflammatory cytokines derived from adipose tissues, and increased deposition of amyloid. They may induce an inflammatory reaction within the islets, as suggested by the presence of infiltrating macrophages and increased IL-1 β (Donath and Shoelson, 2011). Gluco- and lipotoxicity are covered in the Remission of Diabetes in Cats section, and amyloid deposition is covered in the Types of Diabetes in Cats section. In brief, glucotoxicity describes the phenomenon that hyperglycemia per se impairs insulin secretion and possibly leads to β-cell death; similarly free fatty acids increase during the course of diabetes and in turn may cause β-cell damage. Amyloid derives from islet amyloid polypeptide (IAPP), which is co-secreted from the β-cell with insulin. Either the mature insoluble amyloid fibrils lying outside the β-cell or, more likely, small oligomers within the cell may contribute to the progressive β-cell damage (Alsahli and Gerich, 2010).

Other Specific Types of Diabetes and Gestational Diabetes

The category "other specific types" refers to diabetes that develops in association with diseases or factors other than those described under type 1 or type 2 diabetes mellitus. A large number of genetic syndromes, which have not been described in animals, are listed in this category. One example is the maturity-onset of diabetes of the young (MODY), which is inherited in an autosomal dominant pattern. Diabetes may occur secondary to disorders of the exocrine pancreas, and any process that diffusely injures the pancreas can cause diabetes (e.g., pancreatitis, trauma, infection, or pancreatic carcinoma). Several endocrinopathies (e.g., hypersomatotropism, hyperadrenocorticism, hyperthyroidism, pheochromocytoma, hyperaldosteronism, and glucagonoma) are associated with excessive secretion of hormones that antagonize the insulin effect. Similarly, the administration of diabetogenic drugs may result in glucose intolerance or overt disease. Diabetes mellitus usually only occurs in humans with pre-existing β-cell defect. A fourth category in the human model is *gestational diabetes*, which is defined as carbohydrate intolerance with onset or first recognition during pregnancy (American Diabetes Association, 2013).

Types of Diabetes in Cats

Type 1 Diabetes Mellitus

Type 1-like diabetes is generally considered to be rare in cats. Lymphocytic infiltration into the islets (insulitis) as a marker of immune-mediated disease has only been described in a few cases (Minkus et al, 1991; Hall et al, 1997). In a recent study, when examining islet lesions in a larger group of diabetic cats against a control population (matched in age, sex, and body weight), a tendency of lymphocytes to be more frequent in diabetic cats was found (in 20% of diabetic cats and in 5% of control cats). The infiltration was usually mild and may reflect an inflammatory situation also known to be present in type 2 diabetes. Only one of the 27 diabetic cats had severe lymphocytic infiltration, which was similar in severity to those described in the two studies mentioned earlier (Zini et al, 2012; Fig. 7-3, *A*). Beta cell and insulin antibodies have so far not been demonstrated in newly diagnosed diabetic cats (Hoenig et al, 2000a).

Type 2 Diabetes Mellitus

It is currently assumed that approximately 80% of diabetic cats suffer from a type 2-like diabetes mellitus, although there are no thorough studies to support this assumption. Nevertheless, most endocrinologists would agree that type 2-like diabetes is the most frequent form in cats. Similar to human type 2 diabetes mellitus, feline type 2 diabetes is a heterogeneous disease attributable to a combination of impaired insulin action in liver, muscle, and adipose tissue (insulin resistance), and β-cell failure. Environmental as well as genetic factors are thought to play a role in the development of both defects (see Fig. 7-2).

Genetic Factors. Genetic factors have just started to be investigated (Forcada et al, 2010). However, most likely similar to humans, diabetes in the cat is a polygenic disease, and many genes will be associated with an increased risk for the disease. The most convincing evidence of a genetic basis comes from studies

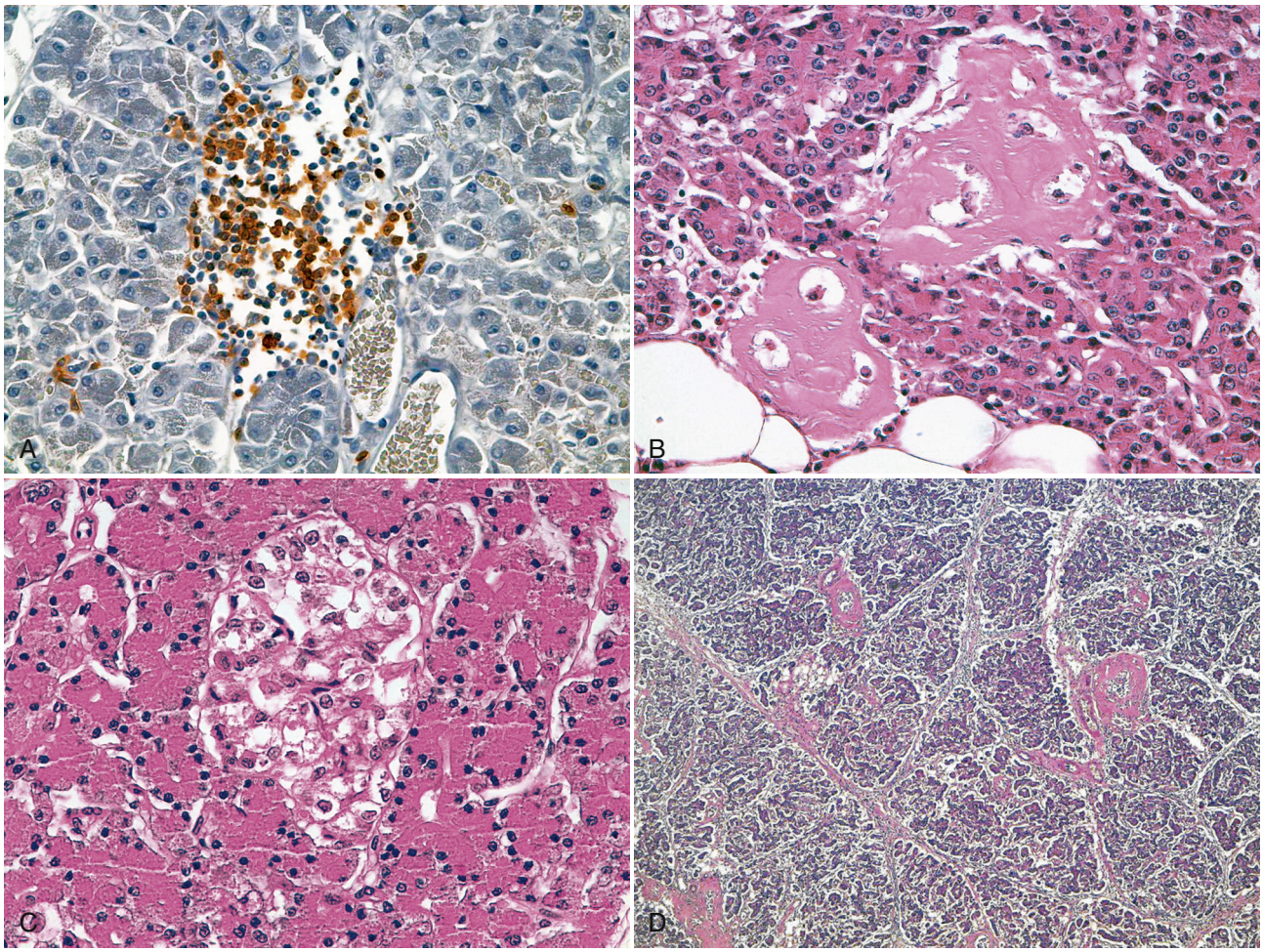

FIGURE 7-3 Pancreatic histology. **A,** Severe infiltration with T lymphocytes within a pancreatic islet in an 18-year-old Domestic Short-Hair (DSH) cat with diabetes mellitus. This is a rare finding, because usually only few or no lymphocytes are found in islets of diabetic cats. Immunohistochemistry for cluster of differentiation 3 (CD3), hematoxylin and eosin (H&E) counterstain (× 40). **B,** Islet amyloidosis in a 16-year-old, spayed female, DSH cat with diabetes mellitus (H&E, × 40). **C,** Vacuolar degeneration of an islet in a 9-year-old, castrated male, DSH with diabetes (H&E, × 40). **D,** Fibrosis in exocrine pancreas in an 8-year-old Siamese cat with diabetes mellitus (H&E, × 40). (From Zini E, et al.: Histological investigation of endocrine and exocrine pancreas in cats with diabetes mellitus, *J Vet Intern Med* 26 (abstract):1519, 2012.)

in the Burmese cat. In breeding lines from Australia, New Zealand, and the United Kingdom, the frequency of diabetes mellitus was shown to be about four times higher in Burmese cats than in domestic cats. In some families of Burmese cats, more than 10% of the offspring were affected by diabetes (Rand et al, 1997; Wade et al, 1999; McCann et al, 2007; Lederer et al, 2009).

Obesity, Gender, and Other Risk Factors. One of the major risk factors for the development of diabetes in cats is obesity. Others are male gender, physical inactivity and indoor confinement, increasing age, and the administration of glucocorticoids and progestagens (Panciera et al, 1990; Crenshaw and Peterson, 1996; Scarlet and Donoghue, 1998; McCann et al, 2007; Prahl et al, 2007; Slingerland et al, 2009). It has been shown that obese cats are 3.9 times more likely to develop diabetes mellitus than were cats with an optimal weight (Scarlett and Donoghue, 1998). Experimental studies in healthy cats showed that an average weight gain of 1.9 kg during a feeding trial was associated with a decrease in insulin sensitivity of more than 50% (Appleton et al, 2001). Similar results were reported in another trial in which each kilogram increase in weight led to approximately 30% loss in insulin sensitivity (Hoenig et al, 2007). Insulin sensitivity differs considerably between individuals, and it was suggested that cats with intrinsically low insulin sensitivity are at increased risk of developing glucose intolerance with weight gain. Male cats tended to have lower insulin sensitivity prior to the feeding trial and gained more weight than female cats, which might explain in part why male cats are at increased risk of developing diabetes mellitus (Appleton et al, 2001). The mechanisms of insulin resistance on a cellular level and the interrelations of the different findings are not yet understood in cats. Most of the research to date has focused on glucose transporters (GLUTs), insulin signaling genes in insulin-sensitive tissues, and secretion of adipocytokines from adipose tissue. In cats that became obese, the expression of the insulin-sensitive GLUT-4 in muscle and fat was significantly lower than in lean cats, whereas the expression of GLUT-1, which is not insulin-sensitive, remained unchanged (Brennan et al, 2004). Expression of several insulin signaling genes in liver and skeletal muscles were significantly lower in obese cats than in lean cats, which is similar in humans with insulin resistance (Mori et al, 2009a).

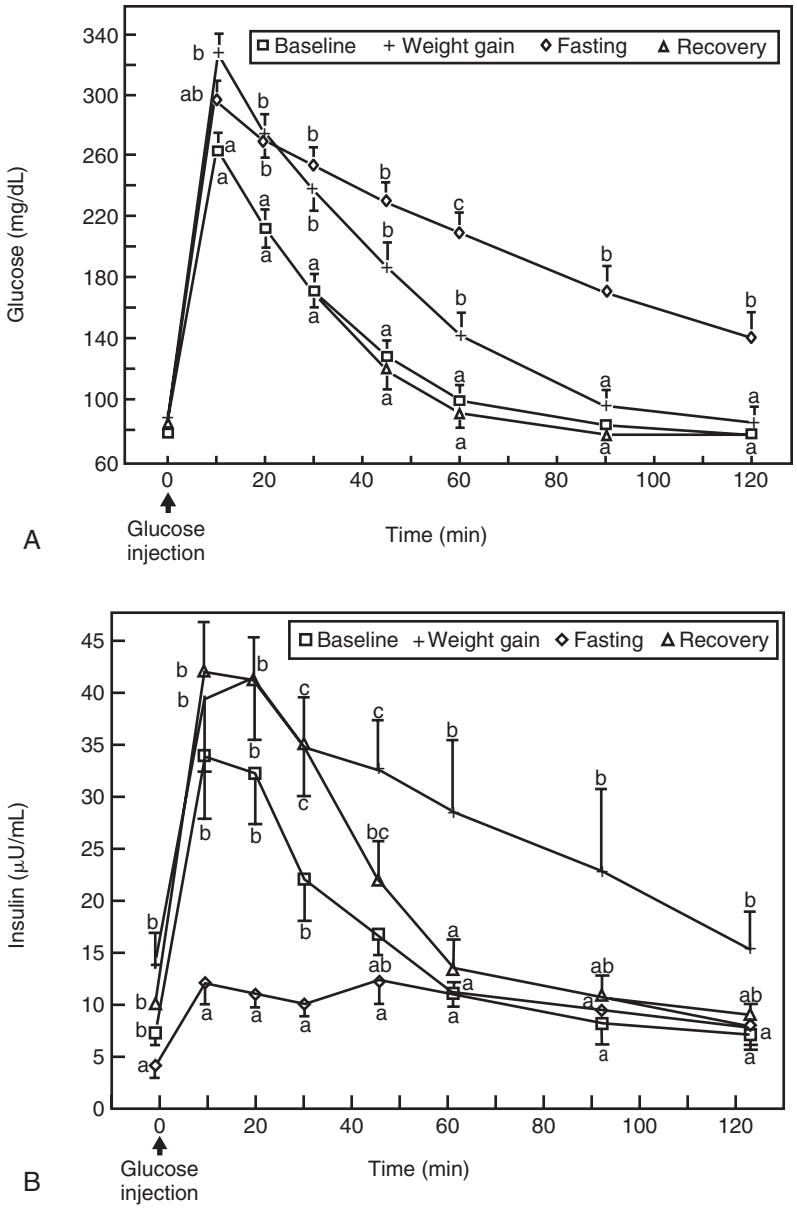

FIGURE 7-4 Mean glucose **(A)** and insulin **(B)** concentrations (± standard error of the mean [SEM]) in 12 cats after intravenous (IV) administration of 0.5 g of glucose per kilogram of body weight at entry into the study (baseline), after 9 ± 2 months of weight gain, after a voluntary fast of 5 to 6 weeks (weight loss), and 5 weeks after the end of fasting (recovery). *a* to *c,* Points with a different letter are significantly different ($p < 0.05$) among periods. Note the development of impaired glucose tolerance despite increased insulin secretion with weight gain and improvement in glucose tolerance and the exaggerated insulin secretory response with weight loss. (From Biourge V, et al.: Effect of weight gain and subsequent weight loss on glucose tolerance and insulin response in healthy cats, *J Vet Intern Med* 11:86, 1997).

Adipokines and Proinflammatory Cytokines. Also similar to humans, it is now recognized in cats that adipose tissue is an active and complex endocrine organ. It was shown that adiponectin, which is almost exclusively produced in adipose tissue, decreases with obesity and diabetes mellitus in cats (Brömel et al, 2004; Hoenig et al, 2007). Adiponectin belongs to the large group of molecules synthesized in adipose tissue and collectively termed *adipokines.* Adiponectin enhances insulin sensitivity and has anti-inflammatory properties; a decrease, therefore, contributes to insulin resistance and inflammation. Leptin, the "prototypic" adipokine, is involved in appetite suppression and energy expenditure and plays a role in modulation of insulin sensitivity (Radin et al, 2009). Obese cats have been found to be leptin-resistant (i.e., they have much higher leptin levels than lean cats without causing an appropriate physiological response) (Hoenig, 2012). As described earlier, it is known in humans that adipose tissue secretes a number of proinflammatory cytokines, and obesity is now considered a state of low-grade chronic inflammation. TNFα was the first adipose-derived factor suggested to represent a link between obesity and the insulin resistance seen in human type 2 diabetes; this cytokine exerts a strong negative influence on insulin signaling. Today, various additional cytokines and chemokines (e.g., IL-6, MCP-1) are known also to be involved in the inflammatory process in humans (Kanaya and Vaisse, 2011). Adipose tissue in cats may behave in a similar manner, because the level of TNFα (in fat) was significantly higher in obese than in lean cats (Hoenig et al, 2006). Further studies, in particular in naturally acquired diabetes, are needed to substantiate those findings. The interested reader is referred to the reviews of Radin, et al., (2009) and German, et al., (2010) for more details on obesity, adipokines, and inflammation. For everyday practice, it is important to know that insulin resistance evolving during weight gain is reversible after weight loss. When healthy cats were fed ad libitum, weight gain was associated with a significant increase in glucose, and insulin concentrations during an intravenous glucose tolerance test (IVGTT) compared to baseline and the total amount of insulin secretion was significantly higher. Several weeks after weight loss was achieved by low caloric intake, the results of the IVGTT were similar to those at baseline (Biourge et al, 1997; Fig. 7-4). The study underscores the importance of weight management throughout life and in particular in cats with diabetes.

Beta-Cell Dysfunction, Amyloid, and Glucotoxicity. It is important to note that although obesity induces insulin resistance, not all obese cats develop diabetes mellitus. Healthy β-cells adapt to obesity and insulin resistance by increasing insulin secretion to maintain normal glucose tolerance (see also Fig. 7-2). Additionally, cats also seem to be able to lower their glucose output from the liver in case of peripheral insulin resistance (Hoenig, 2012). For diabetes to develop, there must be β-cell dysfunction leading to impaired glucose tolerance and eventually type 2 diabetes. Unfortunately, there are nearly no data on β-cell function and insulin secretion in cats during the natural development of diabetes. Most studies were done in healthy cats in which obesity was induced within a short period of time by ad libitum feeding. In one study, cats were made diabetic by pancreatectomy and administration of insulin antagonistic drugs (Hoenig et al, 2000b). From this study one can conclude that in the early stage of diabetes the first phase of insulin release becomes delayed and smaller, whereas insulin secretion during the second phase is more pronounced; during this stage, baseline glucose is still normal. With time, the first phase of insulin secretion disappears almost completely, insulin secretion becomes erratic, and the total amount of insulin during the 2-hour IVGGT decreases substantially. At this time, baseline glucose concentration is increased (i.e., overt diabetes is present). As a reminder: Healthy lean cats have a biphasic insulin secretion pattern when stimulated with glucose during an IVGGT (Hoenig et al, 2000b; Hoenig, 2012).

The big question, "What exactly leads to β-cell failure under natural conditions?" is unanswered until today. One long-known hypothesis concerns β-cell destruction by amyloid deposition. Islet amyloid derives from a hormone named IAPP also known as *amylin.* IAPP is a normal product of the β-cells, which is stored together with insulin in secretory vesicles and is co-secreted with insulin into the circulation. IAPP levels are elevated in conditions associated with insulin resistance (e.g., in cats with obesity) (Henson et al, 2011). Only cats, humans, and nonhuman primates have an amyloidogenic amino acid structure of IAPP with the potential to form amyloid depositions within the islets of the pancreas (O'Brien, 2002; Hull et al, 2004). Amyloid depositions have been found in many cats with diabetes; it is, however, also a frequent finding in non-diabetic cats. In a recent study, 56% of diabetic cats and 42% of control cats matched for age, sex, and body weight had amyloid depositions, the amount of which was also comparable (Zini et al, 2012; see Fig. 7-3, *B*). The situation is similar in humans, because many of the type 2 diabetics, but also a substantial percentage of non-diabetics, have amyloid depositions in the pancreatic islets (Alshali and Gerich, 2010).

The open questions are: "Why aren't all individuals with an amyloidogenic structure of amylin forming amyloid depositions?" and "Is amyloid a cause or consequence of the disease?" It has been shown that disturbed protein folding and/or trafficking of amylin within the β-cells lead to the formation of so-called toxic oligomers. These intracellular molecules induce cytotoxicity and may lead to a decline in β-cell function and to β-cell apoptosis. The extracellular amyloid deposits seem to be less toxic and represent the end point of misfolding (Costes et al, 2013). Loss of β-cell function may therefore be present before amyloid depositions are visible. Opinions on the importance of IAPP/amyloid in the pathogenesis of β-cell failure differ between research groups (in particular in human medicine). It is likely that the misfolding is a reflection of another defect within the β-cells and not the primary cause of β-cell dysfunction. When present, however, these abnormalities may accelerate further damage. An additional factor, which has a negative impact on β-cell function and survival, is high blood glucose concentrations—a phenomenon known as *glucotoxicity.* There is little doubt that glucotoxicity is a secondary event, because hyperglycemia becomes apparent only after β-cells start to fail. However, improving glycemic control by insulin therapy will reverse some of the negative effects, and reversal of glucotoxicity is an important mechanism to explain diabetic remission. *Lipotoxicity* is the term used for the damaging effect of high levels of free fatty acids; in cats, however, lipotoxicity may not be as important as glucotoxicity (Zini et al, 2009a). Details are discussed in the section on remission of diabetes. In humans with type 2 diabetes, inflammatory changes within the islets have been reported, potentially contributing to β-cell apoptosis (Robertson, 2009; Donath and Shoelson, 2011). As mentioned in the beginning of this section, more lymphocytes were found in the islets of diabetic cats than in a matched control population. It was speculated that they may have contributed to the loss of β-cells (Zini et al, 2012). Clearly, more studies are needed to define the role of islet inflammation.

Other Specific Types of Diabetes (Secondary Diabetes Mellitus)

Diabetes in cats may develop as a consequence of another disease or the administration of diabetogenic drugs, such as glucocorticoids and progestins. In humans, this category encompasses various disorders (in particular genetic disorders), which are so far unknown in cats. Some of the subcategories, such as diabetes associated with pancreatic diseases or other endocrinopathies, are known to occur also in cats. These diseases may account for approximately up to 20% of diabetic cases in cats. Diabetes induced by glucocorticoids or progestins is relatively common (see also Concurrent Disorders Causing Insulin Resistance and Drug-Induced Diabetes). The interrelationships of the endocrine and exocrine parts of the pancreas are complex. For instance, acinar tissue is in close contact with the islets without surrounding capsule or basement membrane, and an islet-acinar portal system communicates between both parts (Chen et al, 2011). It is, therefore, easy to understand that a disease in one part will also affect the other one. Pancreatitis has gained a lot of attention during the past years, and it is now known that it is a relatively common disease in cats. The cause and effect of pancreatitis and diabetes in cats, however, is difficult to define and is largely unknown. In previous studies, histological abnormalities consistent with pancreatitis were found in 22% and 51% of diabetic cats. Findings included neutrophilic infiltration and necrosis considered consistent with acute pancreatitis and diffuse lymphocytic and lymphoplasmacytic infiltration considered consistent with chronic pancreatitis (Kraus et al, 1997; Goossens et al, 1998). However, recent histological studies also revealed a high prevalence of pancreatitis in cats without diabetes. De Cock, et al., (2007) performed histological examinations of the pancreas of 115 cats that had been euthanized for various reasons; 41 of them had been clinically healthy. The overall prevalence of pancreatitis was 67%, evidence for chronic pancreatitis was found in 50.4%, for acute pancreatitis in 6.1% of cases, and approximately 10% of cases had both acute and chronic pancreatitis. We recently studied pancreatic tissue of 37 diabetic cats in comparison to tissue from 20 matched control cats using the same histological criteria as De Cock, et al. The findings in control cats were similar to their study, and interestingly, the prevalence of pancreatic lesions in diabetic cats was as high as in the non-diabetic control cats. The overall prevalence of pancreatitis in diabetic cats was 57% and in control cats 60%. Diabetic cats had a trend for more severe lesions and higher prevalence of acute pancreatitis; however, the difference was not significant (Zini et al, 2012). As suggested by De Cock, et al., (2007), the pancreas generally seems to be very sensitive to drugs, stress, metabolic derangements, or ischemia associated with a wide variety of diseases. According to the currently available data and the impression of the author, pancreatitis is not a frequent cause

of diabetes mellitus. Although in principle, severe pancreatitis with extensive tissue destruction may result in damage of the pancreatic islets and β-cell loss, but this seems to be a rare event. Pancreatitis, however, seems to be a frequent comorbidity, and it is very likely that pancreatitis emerges during the course of the diabetic disease. In a substantial percentage of cats, it seems to be a clinical insignificant bystander; in others, it causes clinical signs and may render diabetic regulation at times very difficult. Pancreatitis may also play a role in the development of diabetic ketoacidosis (DKA) (Goossens et al, 1998; Armstrong and Williams, 2012). Diabetes mellitus may also be seen with pancreatic adenocarcinoma; in humans, there is debate as to which diabetes is due to direct effects of the tumor or induced by diabetogenic substances produced by the cancer cells (Chen et al, 2011). Among the endocrinopathies listed under "Other specific types of diabetes" in Box 7-1, hypersomatotropism (acromegaly) and hyperadrenocorticism are the most relevant in cats. Nearly all cats with hypersomatotropism and approximately 80% of cats with hyperadrenocorticism will develop diabetes, which oftentimes is difficult to regulate due to severe insulin resistance. Whereas hyperadrenocorticism is a rare disorder, hypersomatotropism may be present in 10% to 15% of diabetic cats. See Chapters 2 and 11 for more details. In cats, hyperthyroidism and hyperaldosteronism are rarely associated with overt diabetes and pheochromocytoma is extremely uncommon.

In summary, diabetes mellitus in cats is a heterogeneous disease caused by a large number of different factors; the exact etiopathogenic mechanisms are unknown at the moment. The main histological findings within the islets are reduced numbers of β-cells, whereas the other endocrine cells are unaffected; amyloid deposition and vacuolar degeneration, in some of the cats lymphocytic infiltration may be found (see Fig. 7-3, *A* to *D*). Necrosis and fibrosis as well as neutrophilic or lymphocytic infiltration may be present in the exocrine pancreas reflecting acute or chronic pancreatitis.

REMISSION OF DIABETES IN CATS

Remission of diabetes is defined as a situation in which clinical signs disappear, blood glucose concentration normalizes, and insulin treatment (or other antidiabetic drugs) can be discontinued. In human medicine, the duration of normoglycemia has to be at least 1 year to be labelled remission, and prolonged remission is a period of normoglycemia of at least 5 years (Buse et al, 2009). In cats, a cut-off of 4 weeks of normoglycemia has been used (i.e., the disease-free interval should last for at least 4 weeks before the diabetes is considered to be in remission; Sieber-Ruckstuhl et al, 2008; Zini et al, 2010; Tschuor et al, 2011). Prolonged remission may be in duration of at least 1 year. The first publication on 10 cats that had experienced diabetic remission appeared about 15 years ago; at that time the phenomenon was termed *transient diabetes* (Nelson et al, 1999). Interestingly, at the time of diagnosis of the diabetes, baseline insulin concentrations were undetectably low or within the reference range and did not increase after IV glucagon administration, mimicking type 1 diabetes. The cats were treated with insulin or glipizide for 4 to 16 weeks, after which treatment could be discontinued. A second glucagon test, performed after remission had occurred, showed an immediate and significant increase in insulin concentration, insulin peak response, and total insulin secretion compared with initial values; the results of the glucagon test after remission were

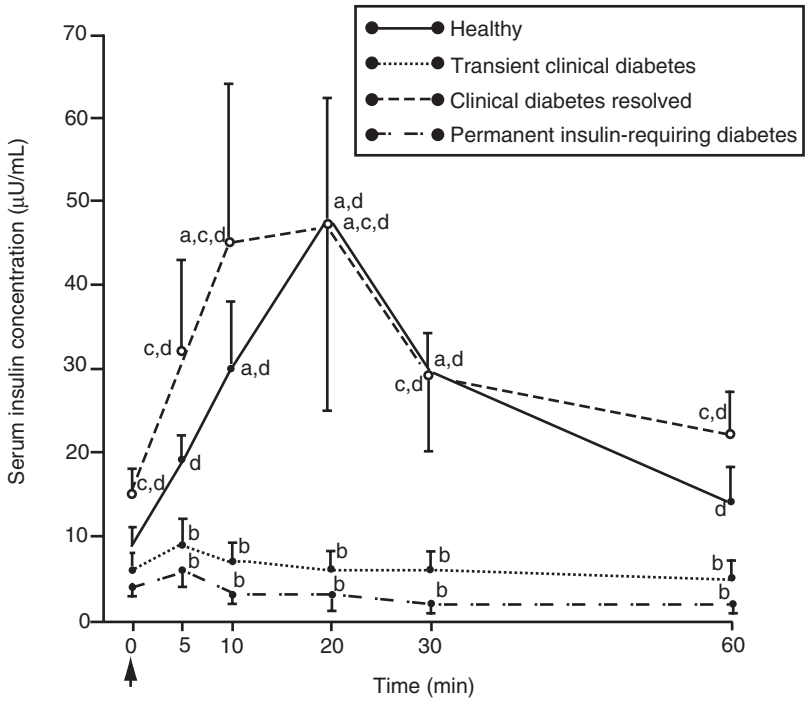

FIGURE 7-5 Mean (± standard deviation [SD]) serum insulin concentrations before and after intravenous (IV) administration of 0.5 mg of glucagon per cat in ten healthy cats—10 cats with transient clinical diabetes at the time clinical diabetes was diagnosed and after clinical diabetes resolved, and six cats with permanent insulin-requiring diabetes at the time diabetes was diagnosed. *a,* Significantly ($p < 0.05$) different compared with baseline value. *b,* Significantly ($p < 0.05$) different compared with corresponding time in healthy cats. *c,* Significantly ($p < 0.05$) different compared with corresponding time when clinical diabetes was diagnosed. *d,* Significantly ($p < 0.05$) different compared with corresponding time in cats with permanent insulin-requiring diabetes. *Arrow* indicates glucagon administration. (From Nelson RW, et al.: Transient clinical diabetes mellitus in cats: 10 cases (1989–1991), *J Vet Intern Med* 13:28, 1999).

similar to test results in healthy cats (Fig. 7-5). Histological evaluation of the pancreas was possible in some of the cats and revealed decreased numbers of islets, islet amyloidosis, and vacuolar degeneration of islet cells. This study demonstrates that initial insulin secretion is severely impaired even in cats with the potential of remission and that the glucagon test performed at the time of diagnosis does not allow differentiation between cats with reversible and cats with irreversible β-cell function. Treatment can lead to improvement of β-cell function, most likely due to abolishment of the damaging effects of high blood glucose on β-cell function (glucotoxicity). The study also showed that cats experiencing diabetic remission are not "cured," because they have islet cell pathology, potentially predisposing them to a relapse of clinical diabetes (Nelson et al, 1999). Since this first report, remission is increasingly recognized, and it is now well accepted that good glycemic control improves β-cell function and that diabetic remission can be achieved in a substantial percentage of cats. Those cats most likely have a type 2-like diabetes resulting from insulin resistance and β-cell dysfunction and some degree of β-cell loss. Their remaining β-cells, however, have the capacity to recover, at least in part, during treatment. Cats that do not experience diabetic remission may be in a more advanced stage of their disease with more pronounced β-cell loss and/or a more pronounced functional defect. Diabetic remission most often occurs during the first 3 to 4 months of therapy; however, remission 1 year and longer after start of therapy may occasionally be seen. The currently available studies, which have included information on remission, are difficult to compare, because they differ with regard to definition of remission, inclusion criteria of cats, blood glucose targets, and monitoring protocols, as well as type of insulin and type of diet. Published remission rates vary between 13% and 100% (Nelson et al, 1999; Bennett et al, 2006; Martin and Rand, 2007; Boari et al, 2008; Michiels et al, 2008; Marshall et al, 2009; Roomp and Rand, 2009; 2012; Hall et al, 2009; Zini et al, 2010; Hafner et al, 2011; Tschuor et al, 2011). It has been suggested that remission rates are higher in cats when treated with newer types of insulin (e.g., insulin analogues such as glargine or detemir) than with other/older types of insulin (e.g., Lente type) (Marshall et al, 2009; Roomp and Rand, 2009; 2012). Although type of insulin and improved time-action profiles of newer insulins may have an important effect on glycemic control and remission rates, other factors such as glucose targets and intensity of monitoring certainly contribute to the high remission rates in some of the studies. For instance, in two recent studies using insulin glargine and detemir respectively, overall remission rates of 64% and 67% were achieved (Roomp and Rand, 2009; 2012). Those studies, however, used an extremely intensive treatment and monitoring protocol: Glucose targets were set very low (50 to 200 mg/dL and 50 to 100 mg/dL respectively; 2.8 to 11.1 mmol/L, 2.8 to 5.5. mmol/L); the owners had to measure blood glucose at home at least three times daily and adapt the insulin dosage accordingly. Those treatment protocols can only be used under very close supervision, because there is an increasing risk of hypoglycemia the lower the glucose targets are set. Low-carbohydrate diets may also contribute to good glycemic control and possible diabetic remission, although data are slim. One study found that remission rate was higher in cats fed a low-carbohydrate diet compared to a moderate carbohydrate diet, whereas in another study, remission rates were similar (Bennet et al, 2006; Hall et al, 2009). However, as mentioned earlier, the studies are difficult to compare because diet composition, type of insulin, and treatment protocols differed. In our own institution, remission rate has varied between 40% and 50% over the years under the following conditions:

- Cats are newly diagnosed with diabetes and have no severe concurrent diseases.
- They are treated according to a standardized treatment protocol, which includes administration of insulin glargine b.i.d. and feeding a low-carbohydrate–high-protein diet.
- Frequent reevaluations are done during the first 4 months of therapy.

Home monitoring of blood glucose has been shown to be advantageous because it allows close supervision and more frequent dose amendments. Remission rates are influenced substantially by which cats are evaluated. In cats with severe concurrent disease or in cats with long duration of diabetes, remission rate will be lower. In cats with previous steroid treatment, remission rates will usually be relatively high. A recent survey among primary practitioners in the United States revealed an approximate remission rate of 26% (Smith et al, 2012). This seems to be a realistic number under an "everyday" condition, in which cats are not preselected and treatment as well as monitoring is more difficult to standardize than in an university environment.

Recently, the question if the capacity of β-cells can be assessed by the time of diagnosis was investigated with the rationale if remission of diabetes can be predicted before initiating therapy. As shown some time ago by Nelson, et al., (1999), no difference in insulin response during glucagon test was seen in cats with and without remission. Studies in humans have demonstrated that the first defect in the early phase of diabetes is a loss response to IV glucose, followed by a loss of response to IV glucagon, whereas response to arginine persists the longest. It was therefore hypothesized that cats that experience remission at some time after starting treatment have less severe β-cell defects than cats with permanent disease and would therefore show normal or at least some degree of insulin response after IV arginine. However, the expectations were not met. In both groups of cats (remission and no remission) insulin concentrations increased mildly after IV arginine, but there was no significant difference between the two groups, similar to what has been shown with the glucagon test (Tschuor et al, 2011; Fig. 7-6). Therefore, none of the tests used so far allows discrimination between cats with and without the chance of remission. A few other studies have evaluated clinical parameters that may be associated with the likelihood of diabetic remission. Interestingly, in a study including 90 cats with newly-diagnosed diabetes, remission rate was shown to increase with increasing age at diagnosis (Fig. 7-7). This finding was unexpected, because it is known that generally β-cell mass decreases with age in healthy individuals. It is possible that in case of diabetes, β-cell destruction is slower in elderly cats, which is similar to what is known from human diabetics (Zini et al, 2010). Other factors shown to be associated with higher likelihood of remission are early treatment of diabetes and prior steroid therapy (Roomp and Rand, 2009). Some factors such as presence of peripheral neuropathy and increased cholesterol have been identified to be associated with reduced likelihood of remission (Roomp and Rand, 2009; Zini et al, 2010). Both may reflect a more advanced state of the disease with more pronounced β-cell loss; hypercholesterolemia may also be a contributing factor to β-cell dysfunction (lipotoxicity). Of note, DKA has not been identified as a negative predictive factor and remission may also occur in cats presented with DKA (Sieber-Ruckstuhl et al, 2008). In many cats, remission lasts for months to years and may even be life-long. Roughly 30% of cats with remission will have a relapse with recurrence of clinical signs and hyperglycemia and will again

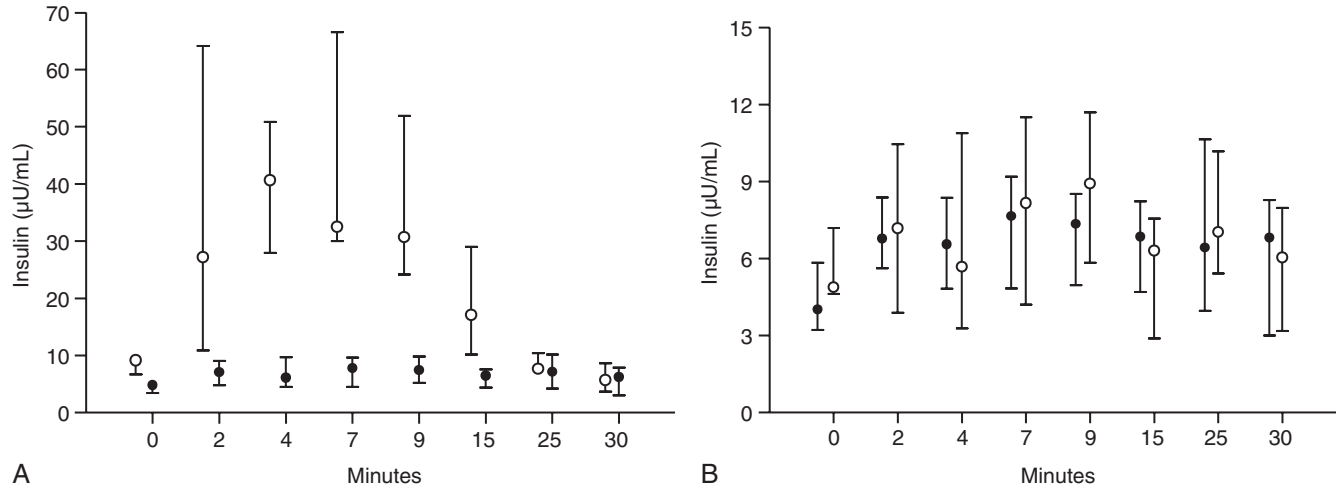

FIGURE 7-6 **A,** Insulin concentration after intravenous (IV) arginine administration in 7 healthy cats *(open circles)* and 17 cats with newly-diagnosed diabetes *(closed circles).* Insulin concentrations in healthy cats were significantly higher 2, 4, 7, 9, and 15 minutes after arginine administrations, where no difference was found between the groups at baseline and after 25 and 30 minutes. **B,** The insulin concentrations of the 17 newly-diagnosed cats shown in **A** were divided into two groups. *Open circles,* 7 cats that experienced diabetic remission during subsequent therapy; *closed circles,* 10 cats with permanent diabetes. The insulin concentrations did not differ at any time point. (Data from Tschuor F, et al.: Remission of diabetes mellitus cannot be predicted by the arginine stimulation test, *Am J Vet Res* 25:83, 2011).

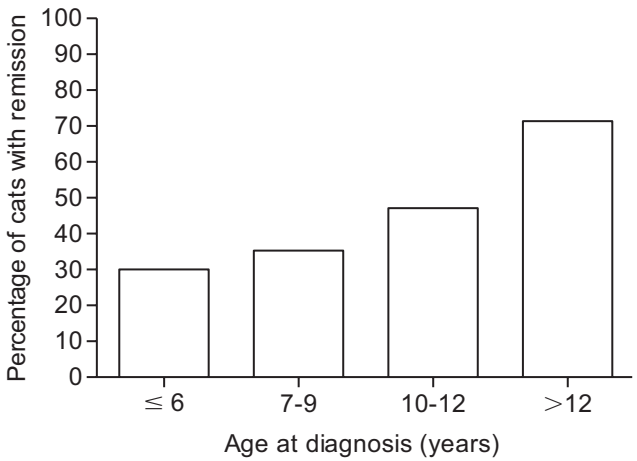

FIGURE 7-7 Percentage of diabetic remission in cats of different ages. It is obvious that remission rates increases with age at the time of diagnosis. Remission rate was approximately 30% when the cats were ≤ 6 years at the time of diabetes diagnosis and remission rate was approximately 70% in cats that were 12 years and older. (Data from Zini E, et al.: Predictors of clinical remission in cats with diabetes mellitus, *J Vet Int Med* 24:1314, 2010).

require insulin therapy. In some of them, a second remission is possible. More often, however, permanent insulin therapy is required. The latter situation most likely reflects deterioration of β-cell function and reduction of β-cell mass.

The damaging effects of chronic hyperglycemia have been known for a long time; nowadays those effects are usually summarized under the umbrella term of *glucotoxicity.* In 1948, Dohan and Lukens administered large doses of glucose to normal cats and induced permanent hyperglycemia, hydropic degeneration of the islets of Langerhans, and ketonuria. It took nearly 50 years for those findings to be recognized in veterinary medicine when Link and Rand (1996) performed a similar experiment. They showed that insulin levels in healthy cats decreased within days when high blood glucose levels were maintained by glucose infusion. Several cats even became ketonuric and required 1 to 2 weeks of insulin therapy after cessation of the glucose infusion (Link and Rand, 1996; Link et al, 2013). The cellular mechanisms by which chronic hyperglycemia affects insulin secretion and insulin sensitivity are poorly understood. In humans, it has been proposed that oxidative stress and inflammatory cytokines play an important role (Robertson, 2009; Donath and Shoelson, 2011).

In a recent study, glucose-induced lesions in β-cells were investigated in cats. After 10 days of IV glucose infusion, healthy cats had 50% fewer β-cells per islet area than control cats. Islet cells showed apoptotic features and were caspase-3 (a marker for apoptosis) positive (Fig. 7-8). Interestingly, hyperglycemia induced a systemic inflammatory response, characterized by an increased plasma concentration of α1-acid glycoprotein. Systemic inflammation has also been described in human type 2 diabetes. Another potential acquired cause of beta-cell dysfunction is lipotoxicity (i.e., the deleterious effects of fatty acids on β-cells). However, in contrast to the 10-day glucose infusion, lipid infusion over the same time period did not affect plasma insulin or glucose levels or result in β-cell apoptosis. In human medicine, it has been proposed that glucotoxicity occurs independently of lipotoxicity, whereas lipotoxicity requires increased blood glucose levels to fully manifest. This may also apply to cats (Zini et al, 2009a).

The concept of glucotoxicity (and possibly lipotoxicity) is very important to understand because immediate treatment of diabetes may reverse the negative effects of glucose on β-cells and increase the chance of remission. Of note, islet cell pathology is present in cats in diabetic remission and remission should not be confused with cure of the disease. Recurrence of clinical overt diabetes is always possible and may be triggered by stressors (increase in body weight, concurrent disease, diabetogenic drugs) or without any obvious event.

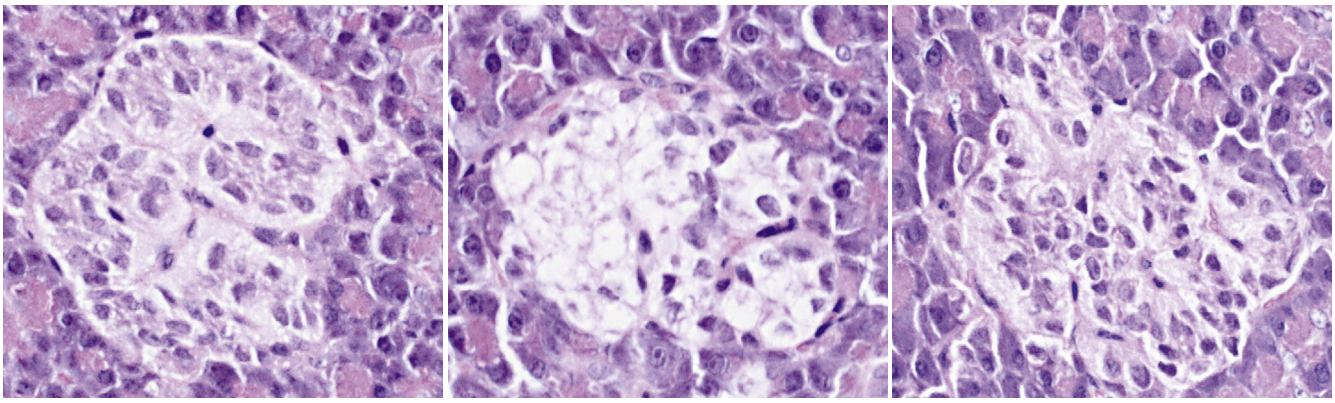

FIGURE 7-8 Pancreatic islets of healthy cats after receiving 0.9% NaCl, intravenous (IV) glucose infusion and IV lipids for 10 days. No lesions were seen in the control cat and in the cat that received lipids. In the glucose-infused cat, a large area of the islet appeared devoid of nuclei and included several vacuoles, which is suggestive of hydropic degeneration. Hydropic degeneration of islet cells indicates accumulation of glycogen. The remaining islet nuclei appear larger than in the control cat. (H&E, × 40) (From Zini E, et al.: Hyperglycemia but not hyperlipidemia causes beta-cell dysfunction and loss in the domestic cat, *Diabetologia* 52:336, 2009a [with permission].)

INSULIN, METABOLIC EFFECTS, AND PATHOPHYSIOLOGY*

Insulin Synthesis, Structure, and Regulation

Glucose homeostasis is maintained by a complex system of regulating and modulating hormones and factors, the most important of which is insulin. Insulin is the only hormone capable of decreasing blood glucose levels.

Insulin synthesis begins in the rough endoplasmic reticulum with the formation of preproinsulin, which is then converted to proinsulin by removal of a small peptide fragment. Proinsulin is further processed to insulin in the Golgi apparatus by removing another peptide, called *connecting peptide (C-peptide)*. Insulin and C-peptide are packed and stored in secretory granules and released in equimolar amounts by the process of exocytosis. Within the granules, insulin co-precipitates with zinc ions to form hexamers and microcrystals, whereas in the circulation, insulin exists as monomer.

Normally, proinsulin conversion is largely completed before secretion and is therefore not encountered in the circulation in appreciable quantities. In human diabetics, increased proinsulin concentrations may be found in plasma, which is considered to be an indicator of β-cell dysfunction (Breuer et al, 2010; Wang and Osei, 2011). Knowledge in cats is limited to obese individuals, which revealed abnormal proinsulin to insulin ratios during IVGTTs (Kley et al, 2008).

Insulin consists of two polypeptide chains: an A chain with 21 amino acids and a B chain with 30, which are connected by two disulfide bridges. The insulin molecule has been highly conserved during evolution, and the differences between species are small. Feline insulin is most similar to bovine insulin, differing by only one amino acid; it differs from canine and human insulin at three and four positions, respectively (Table 7-1).

TABLE 7-1 **DIFFERENCES IN AMINO ACID SEQUENCE OF THE INSULIN MOLECULE BETWEEN SPECIES**

	A8	A10	A18	B30
Human	Thr	Ile	Asn	Thr
Pig/dog	Thr	Ile	Asn	Ala
Cattle	Ala	Val	Asn	Ala
Cat	Ala	Val	His	Ala

Insulin circulates almost entirely unbound in the blood, has a half-life of about 5 to 8 minutes, and is mainly metabolized by the liver and the kidneys (Sjaastad et al, 2010). Continuous availability of insulin and moment-to-moment adjustments are crucial for normal carbohydrate, protein, and lipid metabolism. The body exhibits complex mechanisms to ensure adequate basal insulin secretion between meals as well as increased insulin secretion after a meal. The most important regulator is the glucose concentration in the blood, and there is a positive feedback mechanism between blood glucose concentration and insulin secretion rate.

Glucose is transported into β-cells via the glucose transporter protein GLUT-2, which allows rapid equilibration of extra- and intracellular glucose concentrations. Glucose is metabolized (phosphorylation by glucokinase and production of pyruvate) within the β-cells to produce adenosine triphosphate (ATP). The increase in the ATP/adenosine diphosphate (ADP) ratio is followed by the closure of ATP-sensitive potassium channels in the β-cell membrane, preventing potassium ions from leaving the β-cell. This in turn causes membrane depolarization and opening of voltage-dependent calcium channels in the membrane. The increase in cytosolic calcium then triggers insulin release.

Oral glucose induces a more pronounced insulin secretion than glucose given intravenously. This phenomenon is due to the actions of so-called incretin hormones—the most important

*The section on insulin, metabolic effects and pathophysiology has been published in a similar form in two other book chapters: Reusch CE, et al.: Endocrine pancreas. In Rijnberk A, Kooistra HG, editors: *Clinical endocrinology of dogs and cats,* ed 2, Hannover, Germany, 2010, Schluetersche, pp. 155-185; Reusch CE: Feline diabetes mellitus. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine,* ed 7, St Louis, 2010, Saunders/Elsevier, pp. 1796-1816.

being glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, previously called *gastric inhibitory polypeptide (GIP).* Incretins are secreted by endocrine cells in the gastrointestinal tract in response to nutrients. They are then carried in the bloodstream to the pancreatic islets where they interact with specific β-cell receptors to amplify insulin secretion. GLP-1 has additional effects, which include reduction of glucagon secretion, stimulation of beta-cell differentiation and proliferation, delayed gastric emptying, and induction of satiety (Reusch and Padrutt, 2013).

In addition to glucose and other sugars, amino acids and fatty acids are also stimulators of insulin secretion; stimulation may be direct or potentiated by incretins. The autonomous nervous system modulates islet hormone release; secretion of insulin is stimulated by vagal nerve fibers and inhibited by sympathetic nerve fibers. Several other pancreatic and extra-pancreatic hormones, such as IAPP, glucagon, somatostatin, cortisol, and growth hormone (GH), affect insulin secretion directly or indirectly (Flatt, 2003; Persaud and Howell, 2003; Utzschneider et al, 2004).

Metabolic Effects of Insulin

Insulin regulates numerous metabolic processes through binding to high-affinity cell surface receptors. Like the receptors for other protein hormones, the receptor for insulin is embedded in the plasma membrane. It is a tetrameric protein, composed of two α- and two β-subunits linked by disulfide bonds. The α-subunits are extracellular and house insulin binding domains, whereas the β-subunits penetrate through the cell membrane (Fig. 7-9). The insulin receptor belongs to the large group of tyrosine kinase receptors.

Binding of insulin to the α-subunits triggers the tyrosine kinase activity of the β-subunits leading to autophosphorylation, thus activating the catalytic activity of the receptor. The "substrate" proteins, which are phosphorylated by the insulin receptor, are called *insulin-receptor substrate (IRS) molecules.* They are key mediators in the insulin signaling pathway and act as docking proteins between the insulin receptor and a complex network of intracellular molecules. Dysregulation within the signaling cascade may lead to insulin resistance, and in this context, IRS molecules seem to play a major role.

Within seconds after insulin binds to its receptor, the so-called rapid insulin actions lead to the uptake of glucose, amino acids, potassium, and phosphate into cells. After a few minutes, intermediate actions occur, mainly effecting protein and glucose metabolism, followed several hours later by delayed actions, which mainly include effects on lipid metabolism.

Glucose is a polar molecule and cannot diffuse across cell membranes. Transport of glucose is facilitated by a family of GLUT proteins or by active transport with sodium in the intestine and kidney. Currently, 14 different GLUTs are known for humans, which are named in order of discovery—GLUT 1 to 14. GLUT-4 is the major insulin-responsive transporter and is found almost exclusively in muscle and adipose tissue. Insulin stimulates glucose transport in those two tissues by causing the translocation of GLUT-4 from the cytosol to the cell membrane with which they fuse. There, they function as pores enabling glucose entry. When insulin levels decrease, GLUT-4 is removed from the cell membrane (see Fig. 7-9). In various other tissues (e.g., brain, liver, kidney, and intestinal tract), glucose uptake is insulin-independent and occurs by other GLUT proteins (Garvey, 2004; Thorens and Mueckler, 2010; Barrett et al, 2012).

Insulin is the most important anabolic hormone in the body and prevents catabolism of nutrient stores. Its main function is to ensure storage of glucose as glycogen, amino acids as protein and fatty acids as fat. The primary target tissues for insulin are liver, muscle, and fat. Insulin facilitates the oxidation of glucose to pyruvate and lactate through the induction of enzymes, such as glucokinase, some hexokinases, phosphofructokinase, and pyruvate kinase. Insulin promotes glycogen synthesis in liver, adipose tissue, and muscle by increasing glycogen synthase activity. Gluconeogenesis is decreased by insulin because of the promotion of protein synthesis in peripheral tissues, thus decreasing the amount of amino acids available for gluconeogenesis. Additionally, insulin decreases the activity of hepatic enzymes that are involved in the conversion of amino acids to glucose.

In adipose tissue, insulin promotes the synthesis of lipids and inhibits their degradation. Insulin activates the enzymes pyruvate dehydrogenase and acetyl coenzyme A (acetyl-CoA) carboxylase, which promote the synthesis of fatty acids from acetyl-CoA. Insulin also increases the activity of lipoprotein lipase, an enzyme that is located in the endothelium of capillaries of extrahepatic tissues and promotes the entry of fatty acids into adipose tissue. Inhibition of lipolysis is mediated through the inhibition of the enzyme hormone-sensitive lipase.

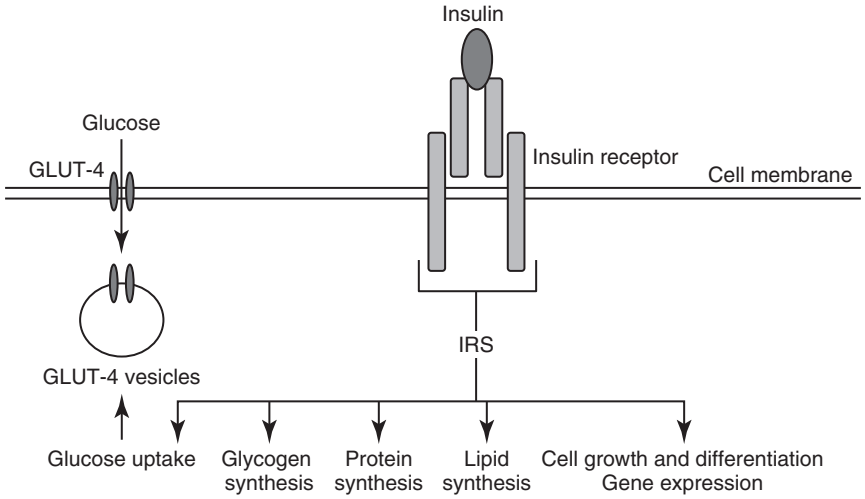

FIGURE 7-9 Simplified scheme of insulin signaling pathways. *GLUT-4,* Glucose transporter 4; *IRS,* insulin receptor substrate.

Insulin stimulates protein synthesis and inhibits protein degradation, therefore promoting a positive nitrogen balance. Glucagon is the main antagonist of insulin. It acts predominantly on the liver where it increases gluconeogenesis and glycogenolysis and decreases glycogen synthesis. It is also a ketogenic hormone, because of its ability to enhance lipolysis. Insulin and glucagon act in concert after ingestion of protein. Both hormones are released when the concentration of amino acids increases in the plasma. Insulin leads to a decrease in blood glucose concentration in concert with a decrease in amino acid levels. Glucagon counterbalances the decrease in glucose concentration by stimulation of hepatic gluconeogenesis. This interaction allows growth and survival with diets containing almost exclusively protein and fat.

Pathophysiology

Hyperglycemia develops when insulin secretion is absent or inadequate for the degree of insulin resistance. Absolute or relative lack of insulin has profound effects on carbohydrate, fat, and protein metabolism. Hyperglycemia results in part from reduced glucose entry into muscle, adipose tissue, and liver. Intestinal absorption of glucose and glucose entry into brain, kidney, and erythrocytes are not affected. The second and perhaps most important cause of hyperglycemia is unopposed glucose production in the liver (by gluconeogenesis and glycogenolysis). Glucagon contributes to increased production of glucose, as do other (stress) hormones. When the renal capacity for glucose reabsorption is exceeded, glucose is lost in the urine. The resulting osmotic diuresis is compensated by increased water intake, which may lead to severe polydipsia. Diabetic polyphagia is regulated by central mechanisms, in which ghrelin-signaling and other pathways are important. Derangement of lipid metabolism plays a major role in the development of diabetes mellitus and its complications. Intracellular deficits of glucose and lack of insulin lead to acceleration of lipid catabolism. Increased levels of NEFA are transported to the liver, where they undergo β-oxidation to produce acetyl-CoA, the amount of which may exceed the capacity for further oxidation. This results in a shift to ketone body production and may lead to the development of ketoacidosis. An increased hepatic concentration of fatty acids also results in enhanced hepatic synthesis of triglycerides and very–low-density lipoproteins (VLDLs). The consequences are hepatic steatosis and hyperlipidemia.

Protein metabolism shifts towards decreased protein synthesis and increased proteolysis. The increased availability of amino acids further accelerates hepatic gluconeogenesis. Consequences are negative nitrogen balance, loss of muscle mass, and possibly cachexia (Fig. 7-10).

SIGNALMENT

Most cats with diabetes mellitus are older than 4 years of age at the time of diagnosis, although the disease may occur at any age. Juvenile onset of diabetes (i.e., diabetes during the first year of age) is a rare event. In a recent study involving 2576 cats with diabetes mellitus in the United States, only 1.3% of cats were 1 year old or younger, another 1.3% were between 1 and 2 years old, whereas nearly 50% of the cats were between 10 and 15 years old (Prahl et al, 2007; Table 7-2). There is a male predominance; in two large studies from the United States and the United Kingdom, 63% and 65% of diabetic cats were male. It is not yet clear if neutering (in both sexes) is associated with an increased risk of diabetes; in the study performed in the United Kingdom, neutered cats were more likely to be diabetic than intact ones, whereas this was not the case in the study performed in the United States (McCann et al, 2007; Prahl et al, 2007). The vast majority of diabetic cats are mixed-breed cats (i.e., Domestic Short-Hair and Domestic Long-Hair). In some countries (e.g., Australia, New Zealand, and the United Kingdom), the Burmese breed has been shown to be at increased risk (Wade et al, 1999; McCann et al, 2007; Lederer et al, 2009), whereas this risk seems not to be present in breeding lines of other countries. In our own population of diabetic cats, approximately 50% to 60% are overweight, 30% to 40% are normal weight, and 5% to 10% are underweight (Reusch, 2010). For more details on prevalence and risk factors, see Prevalence and Risk Factors in Humans and Cats at the beginning of the chapter.

TABLE 7-2 **AGE OF 2576 CATS WITH DIABETES MELLITUS FROM THE VETERINARY MEDICAL DATA BASE JANUARY 1, 1970, THROUGH DECEMBER 31, 1999**

AGE (YEARS)	NUMBER OF CATS	PERCENT
≤ 1	32	1.3
1 to 2	34	1.3
2 to 4	83	3.3
4 to 7	288	11.3
7 to 10	570	22.5
10 to 15	1220	48.1
> 15	311	12.2

From Prahl A, et al.: Time trends and risk factors for diabetes mellitus in cats presented to veterinary teaching hospitals, *J Feline Med Surg* 9:351, 2007.

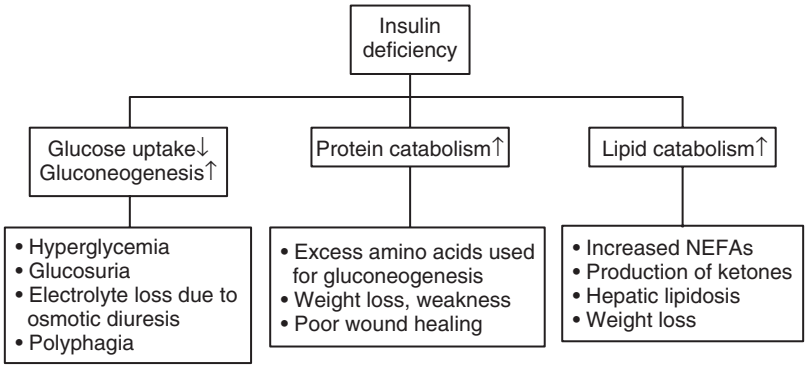

FIGURE 7-10 Effects of insulin deficiency (simplified overview). *NEFAs,* Non-esterified fatty acids.

ANAMNESIS

The typical history includes the classic signs of polydipsia, polyuria, polyphagia, and weight loss. A common complaint of cat owners is the need to frequently change the litter and an increase in the size of the litter clumps, indicating polyuria. Oftentimes, additional clinical signs are present, such as lethargy, decreased interaction with family members, lack of regular grooming, and the development of a dry, lusterless, and unkempt hair coat. Generally, severity of clinical signs ranges between mild/moderate to severe depending on the duration and extent of the diabetic disease. Approximately 10% of diabetic cats have overt signs of diabetic neuropathy, which include hind limb weakness, decreased ability to jump, and a plantigrade posture while standing or walking. Usually, those signs are restricted to the hind limbs; on rare occasion, additional weakness and plantigrade stance may be seen in the front legs. Some owners may overlook the more typical signs of diabetes and the cat is presented because of "lameness" or difficulty to walk and jump. Different to dogs, cats with diabetes are almost never presented because of sudden blindness caused by diabetic cataract. Interestingly, however, the vast majority of diabetic cats reveal some degree of cataract when a specific ophthalmic examination is performed (for details see Chronic Complications of Diabetes Mellitus; Williams and Heath, 2006). In diabetic cats with concurrent disease, additional or other than the classical signs may be reported by the owner. For instance, cats with concurrent pancreatitis may show reduced appetite or complete lack of food intake, some show vomiting, whereas diarrhea is rare. If the clinical signs of uncomplicated diabetes go unnoticed by the owner, a diabetic cat may be at risk to develop DKA. In such a case, the classical clinical signs of diabetes usually are no longer present at the time of presentation. Cats with DKA have similar signs as cats with pancreatitis (both problems often occur in concert), such as lethargy, anorexia, and vomiting; water intake may also be reduced. The time sequence from the onset of diabetes to the development of DKA is unpredictable, ranging from weeks to months and depends in part on the type and severity of any concurrent disease. A complete history is of utmost importance, and the clinician should always consider the possibility of concurrent disorders. Any disorder may reduce insulin sensitivity and may potentially lead to overt diabetes in predisposed animals. Similarly, a detailed medical history should be taken as glucocorticoids (systemic and topical) and progestagens have diabetogenic effects (see Fig. 7-2). Identification and treatment of concurrent disorders and cessation of diabetogenic drugs play major roles in the successful management of the diabetic cats. Dietary history and feeding management (meal or continuous feeding) should also be taken.

PHYSICAL EXAMINATION

The findings during the physical examination depend on the duration and severity of the diabetic disease as well as the presence or absence of DKA and the nature of any concurrent diseases. Cats with recent onset of diabetes or in which severity of diabetes is mild may appear clinically normal and physical examination may be more or less unremarkable. In contrast, cats with long-duration of untreated diabetes may appear seriously ill, in particular if DKA is present. Many newly diagnosed diabetic cats are overweight, although they usually have lost weight. They are rarely emaciated unless a serious concurrent disease (e.g., exocrine pancreatic insufficiency, pancreatic neoplasia, inflammatory bowel disease, or hyperthyroidism) is present. It is helpful to characterize the cats according to one of the currently available body scoring systems (e.g., a 5- or 9-point scale) at initial evaluation and during all rechecks (Fig. 7-11). The same system should be consistently used by all doctors and staff of the hospital. It should be noted that the commonly-used body condition scoring (BCS) focuses mainly on the determination of body fat through evaluation of body silhouette and palpation of adipose tissue (Laflamme, 1997; Michel et al, 2011). Loss of muscle mass may be missed or underestimated or only detected in seriously underweight cats. Assessing muscle condition, however, is important, because loss of muscle adversely affects strength and immune function and has been shown to be independently associated with mortality in humans (Baldwin et al, 2010). Evaluation of muscle mass should be done additionally to the determination of the BCS. It includes visual inspection and palpation over the temporal bones, scapulae, lumbar vertebrae, and pelvic bones. Currently, a 4-point scale is used to assess muscle mass, ranging from normal muscle mass, to mild, moderate, and marked muscles wasting (Baldwin et al, 2010; Michel et al, 2011). See the "AAHA Nutritional Assessment Guidelines for Dogs and Cats" for further details (Baldwin et al, 2010). Diabetic cats may be lethargic, although this may not be obvious immediately if the cat is severely stressed in the examination room. Cats with newly diagnosed or poorly controlled diabetes often stop grooming and develop a dry, lusterless, and unkempt hair coat. The vast majority of diabetic cats show nerve lesions similar to those seen in humans with diabetic neuropathy when histological examinations of peripheral nerves are performed. Obvious clinical signs, however, are present only in approximately 10% of cases. Abnormalities include weakness in the hind limbs, inability to jump, ataxia, muscle atrophy, and a plantigrade posture when standing and walking (Fig. 7-12). A palmigrade posture may also be seen in rare cases. Cats may be object to touching and palpation limbs or feet, presumably because of pain associated with the neuropathy. Findings during neurological examination include postural reaction deficits and decreased tendon reflexes of different severity. Subtle neurological changes may go unnoticed if the cat's gait is not evaluated carefully and no thorough neurological examination is performed. See Box 7-2 and Chronic Complications of Diabetes Mellitus for further details.

Abdominal palpation may reveal hepatomegaly due to diabetes-induced hepatic lipidosis. In cats with concurrent pancreatitis, a mass in the cranial abdomen, consisting of pancreas and inflamed peripancreatic fat, can sometimes be palpated. This mass can easily be misdiagnosed as another intraabdominal structure (e.g., neoplasia within the intestinal tract, enlarged mesenteric lymph node). Palpation may or may not elicit a response of pain. Severe acute or acute on chronic pancreatitis may be associated with dehydration, tachycardia, tachypnea, and icterus; cats may be hypothermic; fever is also possible but less common (Armstrong and Williams, 2012; Caney, 2013). For more details on pancreatitis, see Types of Diabetes in Cats and the discussion on pancreatic enzymes in Clinical Pathology. Similarly, in cats with DKA, severe lethargy, dehydration, abdominal pain, and icterus may be present. Pancreatitis and DKA oftentimes occur in concert.

Lens opacities associated with diabetic cataract are usually mild and only visible by ophthalmoscopy in most cases. More severe cataracts may be present in diabetic kittens compared with adult cats with diabetes (Thoresen et al, 2002; Williams and Heath, 2006).

FIGURE 7-11 Three cats with newly-diagnosed diabetes mellitus and different body condition scores using a 9-point scale. **A,** An example of a relatively normal looking diabetic cat. **B,** A severely overweight cat. **C,** An underweight cat. **A,** Domestic Short-Hair (DSH), spayed female, 13 years old with a body weight of 4.2 kg and a body condition score (BCS) of 5/9. The cat suffered from polyuria/polydipsia, polyphagia, and some weight loss for approximately 4 weeks before presentation. The cat was clinically well, initial blood glucose concentration was 468 mg/dL (26 mmol/L), and fructosamine concentration was 636 μmol/L. **B,** British Shorthair cat, castrated male, 12 years old with a body weight of 8 kg and a BCS of 9/9. The presenting complaint was polydipsia. The cat was slightly lethargic, initial blood glucose was 223 mg/dL (12.4 mmol/L), and fructosamine was 615 μmol/L. **C,** Norwegian Forest cat, castrated male, 14 years old with a body weight of 4.8 kg and a BCS of 3/9. The cat had lost 2 kg of body weight during the previous 2 months, and more recently, the owner had noticed polyuria and polydipsia and reduced appetite. He was dehydrated and had a poor hair coat, initial blood glucose concentration was 509 mg/dL (28.3 mmol/L), and fructosamine concentration was 706 μmol/L. Lipase activity and feline pancreas-specific lipase (Spec fPL) were slightly increased, and ultrasonographic findings were consistent with chronic pancreatitis of moderate severity. After initiating insulin therapy the clinical condition improved and body weight increased.

FIGURE 7-12 Plantigrade stance due to diabetic neuropathy in a 15-year-old, castrated male, Domestic Short-Hair (DSH) with diabetes mellitus. The gait improved slightly during insulin therapy.

ESTABLISHING A DIAGNOSIS OF DIABETES MELLITUS

A diagnosis of diabetes mellitus is based on the presence of appropriate clinical signs (i.e., polyuria, polydipsia, polyphagia, weight loss) and documentation of persistent fasting hyperglycemia and glycosuria. In contrast to human medicine, no precise diagnostic criteria for feline diabetes have so far been established. Therefore, the cut-off value for blood glucose concentration, above which the animal is considered diabetic, is somewhat vague. The vast majority of cats are not presented until blood glucose concentrations exceed the renal capacity for glucose reabsorption (approximately 270 mg/dL, 15 mmol/L). It is usually only at this stage of the disease that clinical signs become apparent. Glycosuria alone is insufficient to diagnose diabetes, because it may also occur with primary renal defects and some of the commercially available urine reagent test strips and tablets may show false positive results associated with

BOX 7-2 Criteria for Neurological Assessment of Severity of Signs and Determination of Severity Rank of Nondiabetic and Diabetic Cats

Severity of Neurological Signs	Criteria
Very mild	• Walks with base-narrow gait • Difficulty in jumping • No evidence of plantigrade stance • Normal postural reactions and reflexes
Mild	• Irritable when touching and manipulating feet • Partially plantigrade, partially crouched limb position • Mild postural reaction deficits • Normal tendon reflexes
Mild/moderate	• Irritable when touching and manipulating feet • Base-narrow gait • Partially plantigrade when walking and standing • Moderately decreased postural reactions and reflexes • Normal tendon reflexes
Moderate	• Irritable when touching and manipulating feet • Plantigrade when walking and standing • Mild generalized muscle atrophy • Decreased postural reactions • Mildly to moderately decreased tendon reflexes
Moderate/severe	• Irritable when touching and manipulating feet • Obvious ataxia and paresis, especially in pelvic limbs • Palmigrade and plantigrade when standing • Plantigrade when walking • Generalized muscle atrophy • Severe postural reaction deficits • Hyporeflexia to areflexia
Severe	• Irritable when touching and manipulating feet • Obvious generalized ataxia and paresis • Palmigrade and plantigrade when standing • Fully palmigrade and plantigrade when walking • Generalized muscle atrophy • Severe postural reaction deficits • Hyporeflexia to areflexia

Modified from Mizisin AP, et al.: Neurological complications associated with spontaneously occurring feline diabetes mellitus, *J Neuropathol Exp Neurol* 61:872, 2002.

the administration of drugs (e.g., some antimicrobials) (Rees and Boothe, 2004). Cats are prone to stress-induced hyperglycemia, which may be difficult to differentiate from hyperglycemia due to diabetes. Increases in blood glucose caused by stress are often only mild to moderate. However, in some cats, blood glucose may increase to levels higher than 270 mg/dL (15 mmol/L) (Rand et al, 2002; Laluha et al, 2004). In a recent study, blood glucose levels in 106 cats with stress hyperglycemia ranged from 146 to 592 mg/dL with a median of 192 (8.1 to 32.9 mmol/L, median 10.7), 21 of the 106 cats (20%) had glucose levels higher than 270 mg/dL (15 mmol/L). Although blood glucose concentrations in cats with stress hyperglycemia were significantly lower than in cats with diabetes, substantial overlap was seen (Laluha et al, 2004; Fig. 7-13). In cats with mild to moderate stress hyperglycemia, glycosuria usually does not occur. However, if stress induces an increase of blood glucose above the renal threshold for some time (hours), glycosuria may be present as in cats with diabetes. Stress hyperglycemia may be diagnosed by repeated blood glucose measurements and the demonstration of normalized glucose levels. Some cats, however, are stressed throughout the period of hospitalization, and glucose levels remain high. In those cases, the measurement of serum fructosamine may be helpful (see Serum Fructosamine Concentration).

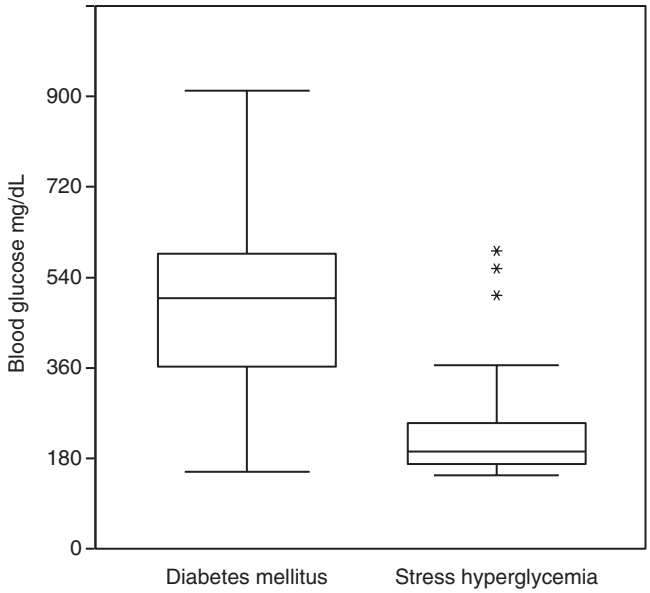

FIGURE 7-13 Blood glucose concentrations in cats with diabetes mellitus and in cats with stress hyperglycemia. Diabetic cats had significantly higher glucose concentrations; however, substantial overlap was seen, and in 20% of the cats with stress hyperglycemia, blood glucose concentrations were increased above the renal threshold. To convert mg/dL to mmol/L multiply by 0.056. (Data from Laluha P, et al.: Stress hyperglycemia in sick cats: a retrospective study over 4 years, *Schweiz Arch Tierheilkd* 146:375, 2004.)

Recently, the term *prediabetes* has started to be used in veterinary medicine. In humans, the term describes individuals whose glucose levels do not meet the criteria for diabetes, yet they are higher than those considered normal (American Diabetes Association, 2013; Table 7-3). So far, there is no officially recognized definition in dogs and cats and the term is somewhat arbitrarily used for any degree of mild hyperglycemia. Cats that have blood glucose concentrations below the renal threshold usually do not have clinical signs of diabetes, and therefore, glucose concentrations between approximately 120 and 270 mg/dL (6.7 to 15 mmol/L) may be considered to represent mild hyperglycemia. Differential diagnosis includes blood glucose increase after a carbohydrate-rich meal, stress hyperglycemia, and mild/beginning diabetes mellitus. Postprandial hyperglycemia may be ruled out by repeating the measurement in a fasted state. Stress hyperglycemia and mild/beginning diabetes mellitus, however, are difficult to differentiate, because fructosamine may be normal in both instances. Normalization of blood glucose concentrations over time is indicative for stress hyperglycemia. Mild/beginning diabetes may have various causes; one of them is the previous or current administration of glucocorticoids or progestagens. In principle, any disease may lead to some degree of insulin resistance and some cats may not be able to compensate by increasing their insulin production (see Fig. 7-2). Cats with mild hyperglycemia should undergo a thorough evaluation and repetitive blood glucose measurements in a fasted state.

TABLE 7-3 **CRITERIA FOR THE DIAGNOSIS OF PREDIABETES AND DIABETES IN HUMANS**

	CRITERIA FOR DIAGNOSIS OF PREDIABETES IN HUMANS	CRITERIA FOR DIAGNOSIS OF DIABETES IN HUMANS
Fasting blood glucose	100 to 125 mg/dL (5.6 to 6.9 mmol/L)	≥ 126 mg/dL (7.0 mmol/L)
2-hour glucose in the 75-g oral glucose tolerance test	140 to 199 mg/dL (7.8 to 11.0 mmol/L)	≥ 200 mg/dL (11.1 mmol/L)

From American Diabetes Association: Diagnosis and classification of diabetes mellitus, *Diabetes Care* 36 (suppl 1):67, 2013.

If no treatable cause is identified, regular reevaluations should be performed to determine if overt diabetes develops. In the stage of "prediabetes," weight reduction and feeding a low-carbohydrate–high-protein diet should be recommended, and insulin treatment should be initiated if blood glucose concentrations begin to rise.

In cats with DKA or severe concurrent disease (e.g., acute pancreatitis), the typical clinical signs of diabetes may not be present at the time of diagnosis, and instead signs of systemic illness will dominate the clinical picture. In those cases, confirmation of diabetes relies on the documentation of hyperglycemia, glycosuria, and increased fructosamine concentration. Immediate further work-up is required, because the animal may be in a life-threatening condition. The finding of ketone bodies in urine by use of urine test strips or increased β-hydroxybutyrate concentration in blood by a handheld meter (Precision Xtra or Precision Xceed, Abbott) is indicative for DKA. Please see Chapter 8 for further details. Diagnosis of pancreatitis is discussed later in this chapter.

CLINICAL PATHOLOGY

After establishing the diagnosis of diabetes, it is important to evaluate the cat for the presence of concurrent diseases. Any disease can worsen insulin resistance and has the potential to render insulin therapy difficult. In some cases, it is only because a concurrent problem occurred that the diabetic disease progressed from a subclinical to a clinically overt state. Reducing insulin resistance by treating the concurrent problem(s) is an important part of diabetic management. The minimum laboratory evaluation in a newly diagnosed diabetic cat should include a complete blood count (CBC), a serum biochemical panel, and an urinalysis with bacterial culture. If available, abdominal ultrasonography should also be performed as part of the routine work-up (see later).

Complete Blood Count, Serum Biochemical Panel, Urinalysis, and Urine Culture

Cats and dogs with diabetes mellitus have similar clinical pathological abnormalities. See Chapter 6 for more details.

In cats with uncomplicated diabetes, a CBC usually does not reveal major abnormalities. Mild normochromic, normocytic anemia (packed cell volume [PCV] 25% to 30%) is a relatively frequent finding, most likely reflecting chronic disease. In dehydrated cats, mild polycythemia may be present, which is frequently associated with an increase in total protein concentrations. Cats with uncomplicated diabetes oftentimes have a normal white blood cell count or a so-called stress leukogram (mature neutrophilia, lymphopenia, eosinopenia). Pronounced neutrophilia, in particular when associated with an increase in immature neutrophils as well as the finding of toxic neutrophils (with or without neutrophilia), points to an inflammatory or infectious process. In the latter situation, the clinician should consider acute pancreatitis as one of the major differential diagnosis. The most common biochemical abnormalities include hyperglycemia, hypercholesterolemia, and increased liver enzyme activities. The vast majority of newly diagnosed diabetic cats have blood glucose concentrations above 300 mg/dL (17 mmol/L); on rare occasions, blood glucose may be as high as 900 mg/dL (50 mmol/L) or even higher. Extremely elevated blood glucose concentrations in diabetic cats are often associated with concurrent chronic renal failure. Between 40% and 50% of diabetic cats have increased serum alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) activities, which is presumably due to diabetes-associated hepatic lipidosis. The increases are typically up to five times the upper limit of normal in cases of ALT and up to three times the upper limit of normal in cases of ALP. More pronounced increases should raise suspicion for hepatic lipidosis being more severe than what is consistent with uncomplicated diabetes, other liver diseases, or pancreatitis. Increased cholesterol and triglyceride concentrations are present in roughly one-third of diabetic cats, which is usually up to three times the upper limit of normal.

A mild increase in total bilirubin concentration (up to two times the upper limit of normal) is quite common and most likely caused by the typical diabetes-associated hepatic lipidosis. If moderate to severe hyperbilirubinemia is present, severe hepatic lipidosis, other liver diseases, or extrahepatic biliary obstruction by pancreatitis should be considered as the most likely causes. Some diabetic cats reveal hypocalcemia, potentially associated with the presence of pancreatitis. Blood urea nitrogen (BUN) and serum creatinine are usually normal in cats with uncomplicated diabetes. An elevation in these parameters may either be due to a prerenal cause (most likely dehydration) or renal disease. In humans, nephropathy is a common complication of diabetes mellitus, whereas in cats, diabetes-associated kidney lesions seem to be rare (see Chronic Complications of Diabetes Mellitus). Chronic renal failure in diabetic cats should therefore be considered a coincidence, because both diseases are relatively frequent in the elderly cat population.

The most typical finding in the urinalysis is moderate to marked glycosuria. Cats with uncomplicated diabetes usually do not have ketonuria; however, trace to small amounts of ketone bodies may occasionally be found. Moderate to large amounts of ketones are indicative of DKA, in particular in cats with signs of systemic illness. In the majority of cats, urine specific gravity is more than 1.020; approximately 50% to 70% of cases have proteinuria, which is usually mild to moderate with a urine protein-to-creatinine ratio less than 2.0. Hematuria, pyuria, and bacteriuria in the urine sediment have been shown to correlate strongly with a positive urine culture. However, in some cats with bacterial urinary tract infection, the urine sediment is unremarkable. Therefore, urine culture should be performed in all cats with diabetes, irrespective of urine specific gravity, presence or absence of proteinuria, and abnormal sediment findings. In two recent studies, urinary tract infection was identified in 12% and 13.2% of diabetic cats, with *Escherichia coli* being the most common isolate (Bailiff et al, 2006; Mayer-Roenne et al, 2007). Urinary tract infections with *Candida spp.* have been reported sporadically in diabetic cats (Pressler et al, 2003; Jin and Lin, 2005).

Pancreatic Enzymes

Pancreatitis has been recognized as a common concurrent disease in cats with diabetes mellitus. Feline pancreatitis is classified into acute and chronic forms, the latter being more common. Some cats suffer from both acute and chronic pancreatitis, and recurrent bouts of acute phases may occur. The cause and effect relationship between pancreatitis and diabetes is largely unknown and very difficult to explore due to the lack of longitudinal studies, which would include histopathology of the pancreas. Severe pancreatitis may result in damage not only of the exocrine but also of the endocrine part of the pancreas, which then would lead to diabetes. Most likely, however, this is a relatively rare event. In the opinion of the author, it is more common for pancreatitis to develop during the course of the diabetic disease. The clinical presentation of pancreatitis varies widely. In some cats, pancreatitis is clinically insignificant with no obvious clinical signs. Other cats suffer from recurrent bouts of pancreatitis ranging from mild lethargy and reduced appetite of a few days' duration to severe illness with complete lack of food intake, vomiting, and dehydration and again others may be constantly unwell. Another subset of diabetic cats suffers from a single episode of severe pancreatitis, which may be severe and life-threatening. Pancreatitis (and/or DKA) should be considered in any diabetic cat presented with lethargy, reduced appetite or anorexia, vomiting, and dehydration. Pancreatitis is also an important differential diagnosis in a difficult to regulate diabetic cat, in particular if the course of the disease is waxing and waning (i.e., times of good glycemic control or hypoglycemia alter with times of poor control). Diagnosis of pancreatitis, however, is challenging, because all available tests have major limitations. Serum amylase activity is often low or normal in cats with pancreatitis and therefore considered to be of no diagnostic value (Kitchell et al, 1986; Parent et al, 1995; Zoran, 2006). Similarly, traditional assays of lipase activity are widely described to be unreliable due to poor sensitivity and specificity. During the recent years, assays that specifically measure the pancreatic lipase activity (known as *fPLI* or *Spec fPL*) became available and are currently considered to be the most accurate blood tests for diagnosing pancreatitis in cats (Steiner et al, 2004; Forman et al, 2009; Armstrong and Williams, 2012). One study reported an overall sensitivity of fPLI for pancreatitis of 67% (100% for moderate to severe pancreatitis and 54% for mild pancreatitis). Overall specificity was 91% (100% in healthy cats and 67% in symptomatic cats with normal pancreatic histology) (Forman et al, 2004). Another study evaluated the Spec fPL and also found 100% sensitivity for severe chronic pancreatitis; specificity, however, was only 54% (Oppliger et al, 2013a). These numbers nicely demonstrate the problems associated with the measurement of the fPLI/Spec fPL test: In cats with severe pancreatitis, the test will usually be positive, whereas it may be negative in mild disease. A positive test result, however, does not mean that the cat has pancreatitis, as specificity is low (67% and 54%). A few studies evaluated fPLI/Spec fPL in cats with diabetes mellitus so far. Prevalence of increased fPLI or Spec fPL was 30%, 43%, and 83% (Forcada et al, 2008; Zini et al, 2011; Schäfer et al, 2013). Interestingly, none of the more than 200 cats showed any clinical signs suggestive of pancreatitis. It is possible that those cats had pancreatic lesions that were not severe enough to cause clinical signs; histopathology, however, was not performed. We do not recommend measuring Spec fPL in cats with uncomplicated diabetes, because any increased value will be difficult to interpret. In diabetic cats with clinical signs suggestive of pancreatitis, diagnosis should be based on the careful assessment of history, physical examination, Spec fPL (or DGGR lipase, see later), additional laboratory findings, and abdominal ultrasonography. In some cats, however, pancreatitis remains a diagnosis by exclusion.

Very recently, the belief that the "normal" serum lipase activity is of no diagnostic utility has been challenged. It was shown in a large number of cats that a particular lipase assay (DGGR assay) agrees substantially with the Spec fPL. The DGGR assay can be performed by routine autoanalysis and therefore be incorporated into a serum biochemical panel rendering lipase measurement more readily available and less expensive (Oppliger et al, 2013b).

Increase in serum fTLI is only very short lived in cats after the onset of pancreatitis and its sensitivity is therefore low. Its measurement is mainly recommended for the diagnosis of exocrine pancreatic insufficiency in the cat, which may develop as a sequela of chronic pancreatitis. Exocrine pancreatic insufficiency should be considered as differential diagnosis in cats with weight loss, polyphagia, and loose stools; a low fPLI would support the diagnosis (Steiner, 2012).

Serum Thyroxine Concentration

Hyperthyroidism is a common endocrine disorder and its prevalence has increased continuously over the last decades. A recent study performed in more than 200 diabetic cats treated with insulin for at least 1 month revealed that 4.5% of them had increased serum thyroxine (T_4) concentrations. This number was considered to approximate the prevalence of hyperthyroidism in the general elderly cat population (Schaefer et al, 2013). Natural occurring and experimentally induced hyperthyroidism has been shown to cause insulin resistance. (Hoenig and Ferguson, 1989; Hoenig et al, 1992). Insulin resistance and possibly impaired insulin secretion is also a well-known phenomenon in humans with hyperthyroidism (Hanley, 2010). The presence of concurrent hyperthyroidism is therefore important to recognize, and the thyroid status should be evaluated in every diabetic cat. When interpreting the laboratory results, the veterinarian should remember that poor glycemic control and any other concurrent diseases may lower the T_4 concentration ("euthyroid sick syndrome") and the diagnosis may be missed. Similarly, in newly diagnosed diabetic cats, T_4 concentrations often are quite low and increase during insulin therapy. This is true for diabetic cats with and without concurrent hyperthyroidism. The latter may therefore be overlooked if T_4 measurements are not repeated after insulin therapy has been performed for some weeks (Fig. 7-14).

In our hospital, we routinely measure T_4 concentrations in newly-diagnosed diabetic cats. Increased T_4 levels support hyperthyroidism and appropriate therapy is initiated additionally to the treatment of diabetes. If the T_4 concentration is normal or low, initial measures are restricted to diabetic management. T_4 measurements are repeated after a few weeks, in particular in cats in which we do not successfully regulate the diabetic disease. We have seen quite a number of diabetic cats in which T_4 measurement had to be repeated several times before hyperthyroidism could be demonstrated. T_4 is also routinely evaluated in all diabetic cats with poor glycemic control, including cats in which glycemic control suddenly deteriorates during therapy. As mentioned earlier, hyperthyroidism lowers serum fructosamine concentrations due to accelerated protein metabolism. Therefore, a low or normal fructosamine concentration or a sudden decrease in fructosamine concentration in a cat with poor glycemic control should alert the veterinarian to the possibility of concurrent hyperthyroidism. Chapter 4 presents a detailed discussion on diagnosis of hyperthyroidism. It also includes information on diagnostic tests that may

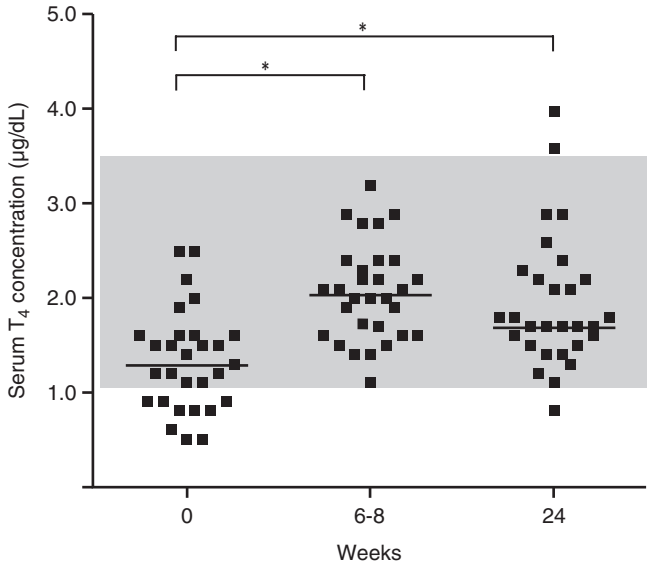

FIGURE 7-14 Serum thyroxine (T_4) concentrations in 30 cats with newly-diagnosed uncomplicated diabetes mellitus. At the time of diagnosis of diabetes, nine of the cats (30%) had T_4 concentrations below the reference range, which normalized after 6 to 8 weeks of insulin therapy. After 24 weeks of insulin therapy, two cats revealed increased T_4 concentrations; those cats were considered hyperthyroid and medical treatment was started. Their initial T_4 concentrations were 2.2 and 2.5 µg/dL, respectively. Reference range: 1.0 to 3.5 µg/dL. To convert µg/dL to nmol/L multiply by 12.87. (Unpublished data from Hafner M, University of Zurich, Switzerland.) * = Significant difference.

be performed in questionable cases (i.e., cats suspected of hyperthyroidism but have normal T_4 concentrations).

Serum Insulin Concentration

Measurement of the serum insulin concentration is not part of the routine work-up in our hospital. In newly-diagnosed diabetic cats, baseline insulin and insulin concentrations after the administration of a secretagogue (e.g., glucagon, arginine) are usually low or low-normal and do not differ between cats in which diabetic remission occurs during subsequent therapy and cats with permanent diabetes (Nelson et al, 1999; Tschuor et al, 2011). Insulin measurements therefore are not helpful to differentiate between an irreversible β-failure and β-cells that have the potential to recover after the negative effects of high blood glucose concentrations (glucotoxicity) have been reversed by insulin treatment. In theory, a high insulin concentration in a newly diagnosed diabetic cat suggests the presence of functioning β-cells and the presence of an insulin-antagonistic disorder. However, as insulin concentrations are low or low-normal in the vast majority of cats at the time of diagnosis, this is not a cost-effective diagnostic procedure. In cases in which insulin measurements are performed, it is of utmost importance that the insulin assay is validated for the cat and that species-specific reference ranges are available. Most commercially available assays are designed to measure human insulin and do not work in the cat due to amino acid differences between human and feline insulin. Recently, an enzyme-linked immunosorbent assay (ELISA) designed to measure feline insulin was validated (Strage et al, 2012). Most assays will cross-react with exogenously administered insulin; therefore, treatment should be withheld for at least 24 hours in cats already undergoing insulin therapy. Insulin withdrawal may, however, put the cat at risk for DKA, in particular in a stressful environment (i.e., in the hospital). The risk should be weighed carefully against any potential benefit. See Remission of Diabetes in Cats earlier and Figs. 7-5 and 7-6 for more details.

DIAGNOSTIC IMAGING

Thoracic and abdominal radiographs play a limited role in the work-up of cats with newly diagnosed diabetes. In uncomplicated cases, hepatomegaly usually is the only relevant finding. Loss of detail or a mass-like effect would raise suspicion for pancreatitis or pancreatic neoplasia. We perform survey radiographs cats in which we suspect the presence of concurrent disease (e.g., cardiorespiratory, skeletal, urolithiasis); this includes cats that are difficult to regulate and cats presented with DKA. In contrast, abdominal ultrasonography is part of our routine work-up in any cat presented with diabetes. Ultrasonography is helpful to investigate size and parenchyma of abdominal organs and abdominal lymph nodes, the bile duct for obstruction, the renal pelvis for dilatation (e.g., in case of pyelonephritis), and the wall thickness and layering of the intestinal tract. In diabetic cats, the pancreas is of particular interest, and ultrasonography is one of the major tools to diagnose pancreatitis. However, visualization of the pancreas is quite difficult and therefore dependent on the experience of the operator and the ultrasonographic equipment. The normal sonographic appearance of the pancreas in cats is isoechoic to slightly hyperechoic to the adjacent liver and nearly isoechoic to the surrounding mesenteric fat. Pancreatitis has various ultrasonographic appearances, depending on the severity, duration of the disease, and extent of pancreatic and peripancreatic inflammation (Penninck, 2008; Fig. 7-15).

Findings associated with acute pancreatitis include enlargement of the pancreas, irregular pancreatic margins, hypoechoic irregular parenchyma, pancreas surrounded by hyperechoic mesentery and/or hyperechoic fat as a result of fat saponification, dilation of the biliary duct, peripancreatic fluid accumulation, and thickening of gastric and duodenal wall, and altered wall layering. Some cats show signs of pain associated with the pressure of the ultrasound probe. Hyperechoic or mixed echogenicity, nodular echotexture, and acoustic shadowing due to mineralization and scarring may be found in cases with chronic pancreatitis. Pancreatic pseudocysts and abscesses may be seen as a sequela to pancreatitis, appearing as round to irregularly marginated fluid-filled mass lesions (Hecht and Henry, 2007). Findings of acute and chronic pancreatitis may overlap, because cats may have acute or chronic disease. The most useful criteria appear to be thickening of the pancreas, severely irregular pancreatic margins, and hyperechoic peripancreatic fat (Williams et al, 2013). It is important to note, however, that the pancreas may also look unremarkable in cats with pancreatitis and that ultrasonographic findings may not correlate with clinical disease. Additionally, the appearance of different pancreatic diseases overlap (e.g., a mass may represent an inflammatory lesion, nodular hyperplasia, or neoplasia). Therefore, ultrasonographic findings need to be interpreted in the light of the clinical situation and laboratory abnormalities.

Reported sensitivity of ultrasonography differs widely between studies; in part this is certainly due to differences in technical equipment and study design. In a study with histological confirmation of pancreatitis, overall sensitivity of abdominal ultrasound was 67% (80% for moderate to severe pancreatitis, 62% for mild pancreatitis) and overall specificity was 73% (88% in healthy cats and 33% in symptomatic cats without pancreatic histology) (Forman et al, 2004). Ultrasonography is also used to guide fine-needle aspiration (FNA), particularly in cats with pancreatic masses. FNA cytology awaits studies to investigate its diagnostic accuracy for

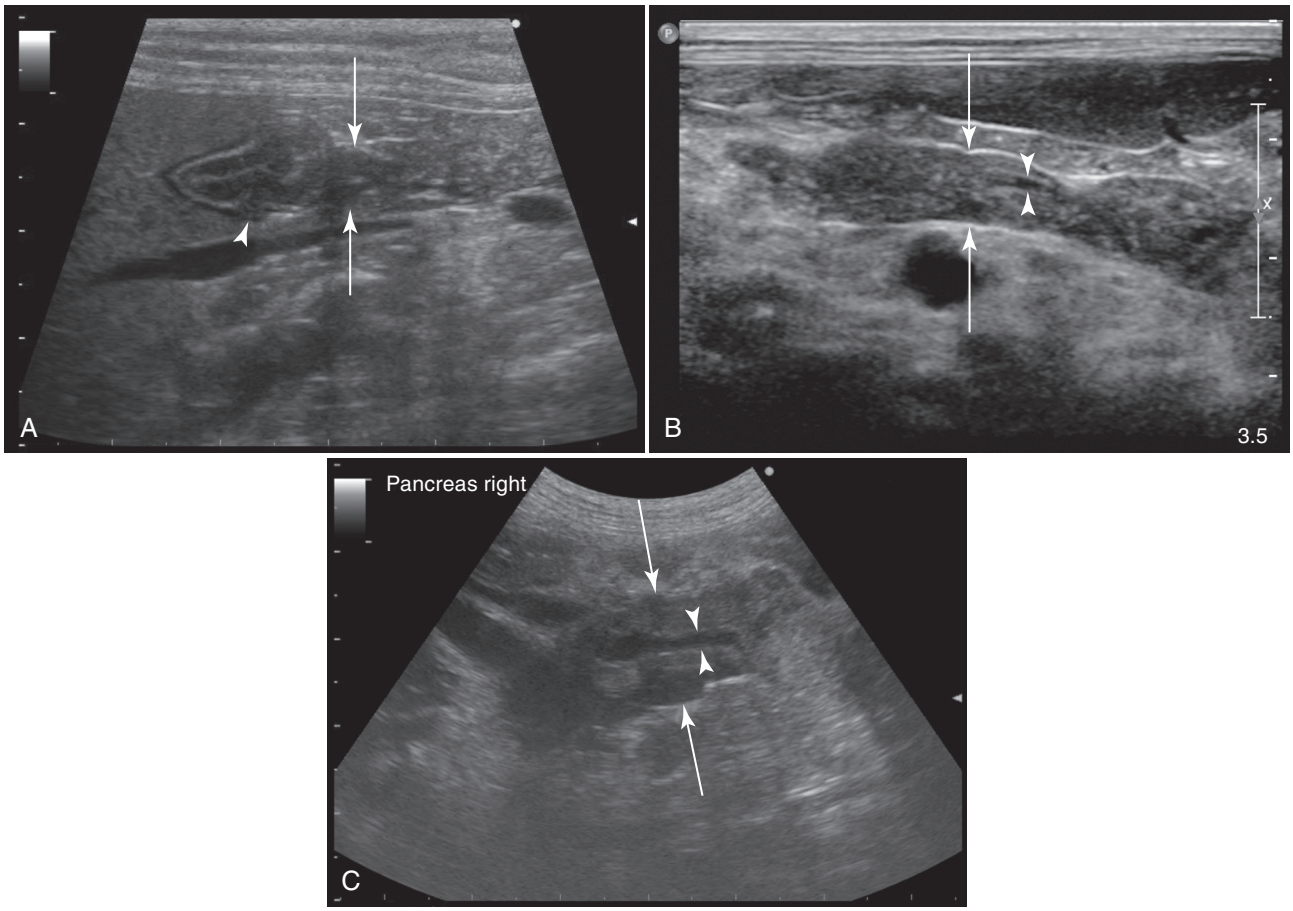

FIGURE 7-15 Ultrasonographic images of the pancreas in three cats with diabetes mellitus at initial presentation. **A,** Siamese cat, castrated male, 7 years old. The pancreas was of normal size, echogenicity was homogenous with smooth margins, and the pancreatic duct was of homogenous width. The pancreas was considered unremarkable. *White arrows* indicate the right branch of the pancreas; *white arrow heads* indicates the papilla duodeni. **B,** Norwegian Forest cat, castrated male, 14 years old (same cat as in Fig. 7-11, *C*). The pancreas was slightly enlarged, echogenicity was heterogenous and slightly hypoechoic, and the pancreatic duct was of homogenous width. Organ margins were slightly irregular. The findings were considered consistent with chronic pancreatitis of moderate intensity. *White arrows* indicate the pancreas; *white arrow heads* indicates the pancreatic duct. **C,** Domestic Short-Hair (DSH), castrated male, 16 years old. Severe diffuse enlargement of the pancreas with mixed echogenicity and irregular margins surrounded by hyperechoic fat was present. The diameter of the pancreatic duct was variable and appeared mildly dilated. The findings were consistent with pancreatitis, which was most likely an overlap between acute and chronic disease. *White arrows* indicate pancreas; *white arrow heads* indicates pancreatic duct. (Courtesy of Dr. Matthias Dennler and Prof. Patrick Kircher, Division of Diagnostic Imaging, Vetsuisse Faculty Zurich, Switzerland.)

the diagnosis of pancreatitis. Knowledge on the value of computed tomography (CT) in the diagnosis of pancreatitis is still scarce. According to currently available studies, its sensitivity seems to be very low (Gerhardt et al, 2001; Forman et al, 2004). We routinely evaluate the adrenal glands in diabetic cats during abdominal ultrasound. Symmetrical enlargement may suggest acromegaly or pituitary-dependent hyperadrenocorticism. An unilateral nodule or a mass may have various causes (see Table 13-5).

TREATMENT OF NONKETOTIC DIABETES MELLITUS

Goals of Therapy

The primary goal in treating nonketotic diabetes mellitus is to eliminate the clinical signs of diabetes, such as polyuria, polydipsia, polyphagia, and weight loss by good glycemic control, to prevent complications (e.g., hypoglycemia, DKA) and thereby enable a good quality of life. Early treatment and good glycemic control is important to increase the chance of diabetic remission. However, this issue requires special attention and one should remember that aggressive insulin therapy and aiming for normal or near normal blood glucose concentrations increases the risk of hypoglycemia. We routinely discuss the possibility of diabetic remission with owners of newly diagnosed diabetic cats. However, we do not stress remission as the major treatment goal for two reasons: to avoid treatment that is too aggressive (i.e., autonomous increase of insulin dose by the owner) and to avoid frustration of the owner if remission does not occur.

Successful treatment requires that the owner is highly motivated, able, and willing to adapt his or her daily routine to the cat's treatment plan and to work in close collaboration with the veterinarian. It may be difficult for some of the owners to understand the nature of the diabetic disease and the various treatment and monitoring

options. Therefore, treatment should follow a precise and comprehensive protocol, and the owner should receive written information on all relevant aspects of the disease and the insulin injection. Short videos demonstrating handling and injection of insulin are also helpful (provided on websites of insulin manufacturers or diabetes forums). Another goal is to minimize the potential negative impact of the cat's disease on the owner and thereby avoid cessation of therapy or euthanasia. Recently, a study evaluated the psychological and social impact of diabetes and its daily treatment regimen on quality of life of both owner and diabetic cat. 221 cat owners from the United States, Canada, Australia, and various countries in Europe completed the survey. The factors with the most negative impact on quality of life were boarding difficulties, owners wanting more control on diabetes, difficulties leaving cat with friends or family, general worry about the cats' diabetes, worried about hypoglycemia, adapting social life, diabetes-related costs, and adapting work life (Niessen et al, 2010). The results of this study may help the veterinarian to address those issues and to make amendments to the treatment and monitoring protocol according to the needs of the individual owner (e.g., simplification of treatment if social life, work life, or costs are the major problems, access to home monitoring of blood glucose if owner wants more control, and avoidance of tight glucose regulation if owner is worried about hypoglycemia).

Treatment of a diabetic cat consists of medical therapy (usually insulin therapy), dietary management (including weight reduction if the cat is overweight), cessation of diabetogenic drugs, and prevention or control of any concurrent disease.

Initial Insulin Therapy

The administration of insulin is the most important part of the treatment regimen in diabetic cats and should be initiated as soon as possible after the diagnosis is established. In humans with type 2 diabetes, initial treatment usually consists of lifestyle modification and oral hypoglycemic drugs. Because many of the cat owners are either diabetic themselves or have diabetic relatives or friends, they tend to ask for those treatment modalities. We then explain our reason for using insulin as first line choice, which is mainly that insulin therapy is superior to the currently available oral hypoglycemic drugs to reverse the negative effects of glucose toxicity and to increase the chance of diabetic remission. In overt diabetes mellitus, dietary management alone is insufficient and may lead to deterioration of the disease and potentially to DKA. Diet, however, is an important part of the treatment.

In the last two decades, the manufacture and development of insulin for human use has undergone revolutionary changes, which have had important implications in veterinary medicine. First, insulins derived from animal sources are being more and more replaced by recombinant human preparations and will eventually disappear from the market. Although there are differences in the amino acid sequences (see Table 7-1) human insulins (and their analogues) are fortunately biologically active in cats. Second, insulin preparations for human use containing 40-IU/mL have largely been replaced by 100-IU/mL insulins. It is important that owners understand the difference, because two insulin preparations for veterinary use (Vetsulin/Caninsulin and ProZinc) are supplied as 40-IU/mL, and using the wrong syringe size would lead to substantial dosing errors. Third, new classes of insulins called *insulin analogues* have been developed. They were designed to improve the pharmacodynamic properties of insulin and render insulin absorption or insulin delivery to tissues more predictable. The currently available insulin analogues are certainly just the start of a whole new area of insulin preparations. The market for insulin can be confusing because insulin availability (particularly if animal-derived) differs between countries as do the names for the same kind of insulin (e.g., Vetsulin is called Caninsulin outside of the United States). Insulin preparations available today may be withdrawn from the market tomorrow. The Internet is helpful to determine the status of a particular insulin (e.g., announcement of withdrawal of Vetsulin starting in 2009 and announcement of its re-approval in April 2013 in the United States).

Insulin preparations are classified as short-acting, intermediate -acting, long-acting, and so-called premixed or biphasic insulins. In principle, more potent insulin preparations have a shorter duration of action than less potent ones (see Fig. 6-30). Short-acting insulin (regular insulin, short-acting analogues such as aspartate, lispro, glulisine) is typically used in cats with DKA, hyperglycemic hyperosmolar state, or with extremely unstable glycemic control. Intermediate and long-acting preparations are used for long-term control of cats with uncomplicated diabetes. The longer duration of action is achieved by slowing the rate of absorption from the subcutaneous tissue. Delayed absorption is due either to the addition of substances that are virtually inert and do not have therapeutic properties themselves (e.g., protamine and zinc) or to a modification of the insulin molecule (as in insulin glargine and insulin detemir). Insulin detemir has some additional protracting effect because it binds to albumin not only in the subcutaneous and extracellular compartment but also in the systemic circulation (Havelund et al, 2004; Owens, 2011). A number of premixed or biphasic insulin formulations are available to facilitate treatment regimens in humans. They are designed to provide a more convenient approach to cover both basal and prandial insulin requirements and consist of a mixture of a short-acting and an intermediate/long-acting component. Ratios of the two components vary (e.g., 75:25, 70:30, and 50:50 intermediate-/long-acting-to-short-acting), premixed preparations are available as insulin analogues or as mixtures of conventional insulin preparations (Bilous and Donnelly, 2010). The use of premixed insulins has so far not been studied in cats. It is likely, however, that they will not be beneficial because cats do not have the same type of postprandial hyperglycemia as humans. See the section on insulin therapy in Chapter 6 for more details on insulin preparations.

Neutral Protamine Hagedorn Insulin

Neutral protamine Hagedorn (NPH) insulin preparations are potent insulins with a marked peak. Unfortunately, duration of action is considerably less than 12 hours in most cats, often resulting in hyperglycemia for several hours during the day. Additionally, the strong peak action increases the risk of hypoglycemia a few hours after administration. The use of NPH insulin is therefore not recommended.

Lente Insulin

A porcine-derived Lente-type insulin (Vetsulin/Caninsulin, Merck/MSD Animal Health) is licensed for use in cats in many countries. It is identical to canine insulin and differs from feline insulin by three amino acids (see Table 7-1). Vetsulin/Caninsulin is available at a concentration of 40 IU/mL, and should be administered twice a day (b.i.d.). Recently, a pen specifically designed to be used with this insulin has been marketed under the name of VetPen. The pen comes in two sizes (0.5 to 8 IU and 1 to 16 IU); the smaller of the two allows insulin dosing in steps of 0.5 units. The pen is used with cartridges containing 2.7 mL (= 108 units) of insulin. Several studies have shown that Vetsulin/Caninsulin is effective and safe for the treatment of diabetes in cats. They are, however, difficult to compare due to the different study

designs. As a rough summary, one may state that approximately 70% to 80% of cats were adequately controlled or diabetic remission was achieved and remission rates varied between 15% and 43%. Clinical hypoglycemia was seen in up to 25% of cats, and biochemical hypoglycemia was seen in more than 40% of cats. The time until the glucose nadir was reached varied substantially and ranged between 2 and 12 hours, and mean/median nadir was reached between 4 and 6 hours (Martin and Rand, 2001; 2007; Weaver et al, 2006; Michiels et al, 2008; Marshall et al, 2009). Vetsulin/Caninsulin is a mixture of 30% to 35% short-acting amorphous and 65% to 70% long-acting crystalline insulin; in theory, this combination should result in a relatively fast onset of action and duration of action of approximately 12 hours. However, in a substantial percentage of cats, the duration of action is considerably shorter, and adequate control cannot be achieved. The recently published American Animal Hospital Association (AAHA) guidelines therefore do not recommend Vetsulin/Caninsulin as the initial insulin option for diabetic cats (Rucinsky et al, 2010). Of note, the manufacturer has recently changed the label and now recommends vigorous shaking the vial prior to first use until a homogenous, uniformly milky suspension is obtained. This should ensure adequate homogenization of the two parts of the insulin, which obviously was a problem with the former recommendation of gently rolling the vial.

Protamine Zinc Insulin

Protamine zinc insulin (PZI) is insulin combined with protamine and zinc. It contains more protamine than NPH and therefore has a longer duration of action. Duration of action is also longer than in Lente insulin (Marshall et al, 2008a). The previous PZI product often used for diabetic cats, which was made from bovine and porcine insulin (PZI-Vet, IDEXX Laboratories), was discontinued some years ago. PZI-Vet was considered a good treatment option; a study reported that 90% of cats had good glycemic control after 45 days of therapy based on owner assessment (Nelson et al, 2001). The gap was filled by the release of ProZinc (Boehringer Ingelheim), which is a recombinant human insulin, formulated as protamine zinc insulin. The level of glycemic control was shown to be similar between the animal-derived and the recombinant product. Good glycemic control was achieved in 85% of cases by the end of the study (day 45). The final median insulin dose was 0.59 IU/kg b.i.d. (range 0.1 to 1.4). The glucose nadir occurred between 1 and 9 hours (mean 4.6); of note in 24% of cats, the lowest blood glucose concentration was at the last blood sampling, and the nadir presumably was later than 9 hours after the insulin administration. A long duration of effect may result in a substantial overlap and potentially hypoglycemia. Clinical hypoglycemia was rare and seen in only 1.5% of cases; biochemical hypoglycemia, however, was a frequent event and seen in 64% of cats at some time during the study period (Nelson et al, 2009). So far, knowledge on remission rates with PZI is scarce. One study reported a remission rate of 38% (Marshall et al, 2009). The AAHA Diabetes Management Guidelines lists ProZinc and Lantus (Insulin glargine, Sanofi) as the two insulin preparations of choice to initiate insulin therapy in cats (Rucinsky et al, 2010). ProZinc contains 40 IU insulin/mL. Contrary to the recommendation for Vetsulin/Caninsulin, the manufacturer of ProZinc recommends mixing by gently rolling the vial. It should be used b.i.d.; in some cats with very long duration of effect, once a day (s.i.d.) administration may be also be effective.

Long-Acting Insulin Analogues

Lantus (insulin glargine, Sanofi) has been the focus of attention in veterinary medicine for several years because of its theoretical benefits, namely a more constant rate of absorption and longer duration of effect compared with several other insulin preparations. Initial studies confirmed that its duration of action is clearly longer than that of Lente insulin and comparable to PZI (Marshall et al, 2008a; 2008b). Recently, the pharmacodynamics of insulin glargine was compared to insulin detemir (Levemir, Novo Nordisk), which is another long-acting insulin analogue. The study was performed using an isoglycemic clamp method, which is considered to be the gold standard method in humans. Performance of the two insulin analogues was similar, the only significant difference was a faster onset of action of insulin glargine (mean of 1.3 hours versus mean of 1.8 hours). Mean time to peak action was 5.3 hours in glargine and 6.9 hours in detemir, and end of action was reached after a mean of 11.3 hours in glargine and 13.5 hours in detemir (Table 7-4). Interestingly, there were considerable variations in the shape of glucose curves; some cats had a flat curve whereas others revealed a pronounced peak (Gilor et al, 2010a). The results from this study compare quite well with our clinical experience made over the past years. Although duration of insulin glargine is quite long, b.i.d. administration is usually required to achieve adequate control or diabetic remission; shape of the glucose curves differ considerably between cats and also within the same cat. So far, insulin glargine has not been evaluated systematically in large clinical trials. A few pilot studies showed that it is safe and effective in diabetic cats and adequate glycemic control can be achieved in many cases. Insulin glargine used over a 4-month period resulted in diabetic remission in 8 of 8 cats (100%), whereas only 3 of 8 cats (38%) treated with PZI and 2 of 8 cats (25%) treated with Lente insulin achieved remission (Marshall et al, 2009). Other studies using insulin glargine were not able to repeat the high treatment success: remission rates ranged between 17% and 47% (Boari et al, 2008; Hall et al, 2009; Hafner et al, 2011). In an Internet-based study using 55 diabetic cats from a German diabetes forum, a remission rate of 64% was achieved (Roomp and Rand, 2009). However, owners were required to measure blood glucose at least three times per day, and insulin dosage was constantly adjusted, which is a regimen suitable for only a selected group of owners. The occurrence of hypoglycemia in glargine treated cats has also not yet been evaluated systematically. In the study by Roomp and Rand (2009), clinical hypoglycemia was reported in only 1 of 55 cats (1.8%), whereas 93% of cats revealed biochemical hypoglycemia at various levels of severity. The latter is certainly mostly associated with the intensive treatment protocol used in the particular study and not with the type of insulin.

There is so far little experience with insulin detemir in diabetic cats. Roomp and Rand (2012) performed a similar study with insulin glargine, again using the intensive treatment protocol and an online German diabetes forum for owners of diabetic cats. The results were similar, remission rate was 67% with insulin detemir;

TABLE 7-4 **PHARMACODYNAMIC PARAMETERS OF INSULIN GLARGINE AND INSULIN DETEMIR**

	INSULIN GLARGINE (Lantus) n = 10	INSULIN DETEMIR (Levemir) n = 10	p-value
Onset of action (h)	1.3 (0.9 to 1.6)	1.8 (1.1 to 2.3)	0.03
Time to peak action (h)	2.5 to 8.0 (5.3)	4.7 to 9.2 (6.9)	0.31
End of action (h)	8.0 to 14.5 (11.3)	11.0 to 16.0 (13.5)	0.18

Modified from Gilor C, et al.: Pharmacodynamics of insulin detemir and insulin glargine assessed by an isoglycemic clamp method in healthy cats, *J Vet Intern Med* 24:870, 2010a.

clinical hypoglycemia was seen in 1 of the 18 cats (6%), whereas biochemical hypoglycemia was common. The starting dose of insulin detemir was similar to the starting dose of insulin glargine in the two studies (0.25 IU/kg of ideal body weight); however, maximal dose of detemir was lower than the maximal dose of insulin glargine (0.5 to 4.0 IU, median 1.75 versus 1.0 to 9.0 IU, median 2.5). Another difference was the relatively frequent development of chronic renal failure in cats treated with insulin detemir. It is unknown so far if this is related to the insulin itself or to the fact that the cats in the detemir study were slightly older than the cats in the glargine study.

Insulin Choice and Initial Dose

The initial insulin of choice depends on personal preference and availability. Cats are unpredictable in their response to insulin and none of the insulin preparations described above are routinely effective to control the disease. We nowadays start treatment in diabetic cats with insulin glargine (Lantus). PZI (ProZinc) would also be a good first choice. Both, insulin glargine and PZI are recommended by the AAHA Diabetes Management Guidelines (Rucinsky et al, 2010). In previous years, we achieved good glycemic control in many diabetic cats using Lente insulin (Vetsulin/Caninsulin), and therefore it may in principle also be used. As mentioned earlier, however, duration of action is often shorter than 12 hours (i.e., shorter than the duration of action of insulin glargine and PZI). If a diabetic cat is well regulated with Vetsulin/Caninsulin, there is no reason to switch it to one of the other insulins preparations. Nearly all cats require insulin twice daily, therefore we always start with b.i.d. administration. The initial dose in cats weighing ≤ 4 kg is 1 IU/cat b.i.d., and in cats weighing > 4 kg it is usually 1.5 IU/cat (–2.0 IU/cat) b.i.d. In cats with a blood glucose concentration < 350 mg/dL (20 mmol/L) at the time of diagnosis, no more than 1 IU/cat b.i.d. is given, independent of the body weight. The starting dose should not exceed 2.0 IU/cat b.i.d., even in a very large cat. It is better to start conservatively (e.g., maximum dose of 1.5 IU/cat b.i.d.), than to risk hypoglycemia during the first few days, which may lead to owner frustration and potentially cessation of therapy. Very small cats (≤ 2 kg) are started on no more than 0.5 IU/cat b.i.d. (Box 7-3).

BOX 7-3 Protocol for the Management of Non-Ketotic Diabetic Cats

Initial Presentation
- Diagnosis of diabetes mellitus (clinical signs, hyperglycemia, glucosuria, increased fructosamine)
- Routine laboratory evaluation (CBC, serum biochemistry panel* urine analysis, urine culture)
- Abdominal ultrasonography
- Cessation of diabetogenic drugs (glucocorticoids, progestagens)
- Start with intermediate-/long-acting insulin
  - First-line: Lantus, ProZinc; second-line: Vetsulin/Caninsulin
  - Initial dose
    - Depends on severity of clinical signs and degree of hyperglycemia; initial dose should not exceed 1.5 to 2.0 IU/cat b.i.d., even in very large cats
    - 0.5 IU/cat b.i.d. if body weight is ≤ 2 kg
    - 1.0 IU/cat b.i.d. if body weight is 2.5 to 4 kg
    - 1.5 IU/cat (– 2.0 IU/cat) b.i.d. if body weight is > 4 kg
- Treatment of concurrent problems (e.g., urinary tract infection, stomatitis/gingivitis)
- Dietary management
  - High protein, low carbohydrate diet; provided that no other disease has priority
  - 45 to 60 kcal/kg/day
  - If overweight, aim for 1% weight loss per week
- Owner instruction (requires at least 1 hour)
- Written instructions for owners

Reevaluation 1 Week after Diagnosis
- Administration of insulin and food at home, and then bring cat to hospital as soon as possible
- History, physical examination, and body weight
- Generation of a BGC (glucose measurement every 2 hours for the remainder of the day, preferentially until next insulin injection, or even thereafter if nadir is not reached)
- Fructosamine measurement
- Adjustment of insulin dosage if required: 0.5 IU/injection. In case of Somogyi effect or overt hypoglycemia, dose reduction of 25% to 50%, depending on the insulin dosage used

Reevaluation 2 to 3 Weeks after Diagnosis
- Repeat all procedures as during first reevaluation
- Introduction to home monitoring, and instruction on all relevant technical aspects (requires at least ½ hour)
- Frequency of home monitoring
  - During initial phases of therapy approximately one BGC per week
  - After stabilization (i.e., when adequate glycemic control is achieved), approximately one BGC every 3 to 4 weeks
  - BGC results should be sent to hospital and dose changes discussed with the veterinarian

Reevaluation 6 to 8 Weeks after Diagnosis
- All procedures as during first reevaluation; BGC may not be required if pet appears clinically well, blood glucose measured close to the time of insulin administration is 10 to 15 mmol/L (180 to 270 mg/dL) and fructosamine is 350 to 450 μmol/L
- Home monitoring results should be assessed and owner technique evaluated
- If glycemic control is inadequate and insulin dose is close to 1 IU/kg b.i.d. or above, further work-up should be pursued

Reevaluation 10 to 12 Weeks and 14 to 16 Weeks after Diagnosis, Then Every 4 Months
- Repeat all procedures done 6 to 8 weeks after diagnosis (except further work-up if not needed)

Goals of Therapy
- Good glycemic control
  - Clinical signs: Resolution of pu/pd, polyphagia, normal body weight
  - Blood glucose: Highest concentration between 180 to 270 mg/dL (10 to 15 mmol/L) and nadir between 80 to 140 mg/dL (4.5 to 7.8 mmol/L)
  - Fructosamine: Ideally between 350 and 450 μmol/L
- Diabetic remission
  - May be achieved in 25% to 50% of newly-diagnosed diabetic cats

*1,2-0-dilauryl-rac-glycero-glutaric acid-ester (DGGR) lipase (part of routine biochemistry panel in some laboratories) or Spec fPL should be measured if clinically indicated.
b.i.d., Bis in die (twice a day); *BGC,* blood glucose curve; *CBC,* complete blood count; *pu/pd,* polyuria/polydipsia.

After diagnosing diabetes mellitus, the cat may be kept in the hospital for 1 to 2 days to complete the work-up. During this time, blood glucose concentration should be measured three to four times throughout the day and the insulin dosage reduced if a low glucose concentration (< 90 mg/dL, 5 mmol/L) is detected. If the blood glucose concentration decreases only slightly, we do not increase the insulin dose because it takes a few days for full insulin action to develop (so-called equilibration). Adjustments in insulin dosage are made on subsequent evaluations. The initial work-up and start of treatment may also be done on an outpatient basis.

The approach is similar in cats that already receive insulin therapy but in which the disease is not adequately controlled. If we consider the type of insulin to be the problem, we switch to a different type, using the same dosing schedule as for the newly-diagnosed diabetic cats. The exception are cats that were shown to be prone to hypoglycemia with the previous insulin, those would not receive more than 0.5 U/cat b.i.d. of the new insulin as a starting dose.

Insulin Handling and Owner Instruction

One of the most important periods in the owner's care of a diabetic pet is the time during which the veterinarian or the technician teaches the technical aspects of the treatment and explains the monitoring protocol. The owner should be instructed to mix the insulin correctly: the manufacturer of ProZinc recommends gently rolling of the vial, whereas Vetsulin/Caninsulin should be vigorously shaken. Lantus (and Levemir) are clear solutions and need no mixing. It should be demonstrated how to load a syringe without air bubbles, and the veterinarian may also refer the owner to one of the many administration videos available through the Internet. We recommend injecting the insulin over the lateral chest wall because perfusion is better there than in the neck area, which increases absorption of insulin. The spot should rotate each time. The owner must understand the differences between U-40 and U-100/mL insulins: ProZinc and Vetsulin/Caninsulin are U 40/mL, whereas Lantus and Levemir are U-100/mL preparations. The use of the correct size of syringe is imperative. The use of non-matching syringes based on conversion tables or the owner's own calculations is discouraged, because the risk of confusion is high. The administration of small doses of insulin is difficult and requires particular attention. For the administration of Lantus (and Levemir) we routinely use 0.3 mL syringes, designed for the application of U-100 insulin preparations in 0.5 IU increments (BD Micro-Fine+Demi U 100 syringes, 0.3 mL, Becton Dickenson); however, for some people a pen designed to deliver 0.5 IU increments may be an alternative. Lantus must not be diluted because dilution changes the time/action profile; Levemir may be diluted with Insulin Diluting Medium for NovoRapid and Levemir supplied by Novo Nordisk (unfortunately it is not available in all countries). Dilution of other insulin preparations has been common practice; however, there are no studies on potential changes of pharmacokinetics and stability. We avoid dilution whenever possible and never dilute Lantus.

Unopened vials should generally be stored in the refrigerator, distant from the freezer compartment. Freezing and heating inactivates the insulin; similarly direct exposure to sun light must be avoided. We also recommend storage of in-use vials in the refrigerator to ensure a consistent environment. However, insulin is also stable at room temperature (as long as it is < 86° F, < 30° C, and light-protected) for approximately 4 weeks, which may be important for travelling. Insulin stored in the refrigerator should be allowed to warm up a bit before injection. Manufacturers declare that opened (in use) vials have to be replaced after 28 (Lantus), 42 (Vetsulin/Caninsulin, Levemir) or 60 days (Pro Zinc); however, true shelf-life is certainly longer and often owners use the insulin for longer times. We routinely inform owners about the potential risk of contamination and loss of activity and that cloudy or discolored vials should be discarded. Similarly the vial should be replaced if glycemic controls inexplicably deteriorate.

Reevaluations and Adjustment of Insulin Dose

After the initial work-up, the cat is discharged with insulin, syringes, diet, and, if needed, treatment for any concurrent disease. We inform the owner about the fact that during the next 3 months, frequent reevaluations and close monitoring are needed. Reevaluations are scheduled as a minimum after weeks 1, 2 to 3, 6 to 8, 10 to 12, 14 to 16, and then approximately every 4 months (see Box 7-3). Additional appointments may be necessary in some cats. It usually takes between 1 and 3 months until adequate glycemic control is achieved, and it is also during the first 3 months that the likelihood of diabetic remission is greatest. The latter should not be overlooked, because serious hypoglycemia may occur. We also introduce the general concept of home monitoring after initial work-up, and our written instructions contain some more information and pictures about the technical aspects. However, we usually wait for 2 to 3 weeks until teaching the technique. We first want to ensure that the owner is able to handle the other parts of the disease (regular insulin injections, change in diet, weight management) until moving on to the next step. The exceptions are highly motivated owners or diabetic owners being familiar with capillary glucose measurements. Ideally, insulin injections should be given every 12 hours; however, this may not be possible for all owners. Therefore, we "allow" shifts of 1 to 2 hours. We always start with the same insulin dose in the morning and in the evening. In some cats, "different" doses may be required during long term management (e.g., a lower dose in the evening if recurrent episodes of hypoglycemia occur at night).

Clinical signs of diabetes usually resolve when blood glucose concentrations can be kept below the renal threshold, ideally the lowest glucose concentration (glucose nadir) should be between 80 and 140 mg/dL (4.5 to 7.8 mmol/L), the highest glucose concentration between 180 and 270 mg/dL (10 to 15 mmol/L). At each reevaluation, the owner is questioned about his/her opinion on the cat's overall health, water intake, urine output, a thorough physical examination is performed, body weight is recorded, and a serial blood glucose curve (BGC) is generated. Fructosamine measurement may also be informative. If glycemic control is considered unsatisfactory, the insulin dose is increased in steps of 0.5 IU/cat per injection. It is possible that the insulin dose has to be increased several times until a reaction (clinically and with regard to blood glucose concentration) is seen. We usually make dose changes no more often than every 5 to 7 days. It is also possible that the type of insulin has to be changed. If duration of action is too short, a longer acting insulin should be used and vice versa. As mentioned earlier, Vetsulin/Caninsulin usually has a shorter duration of action than ProZinc and Lantus; in some cats, ProZinc may have a longer duration of action than Lantus, although there is variability between cats. Levemir seems to have a slightly longer duration of action than Lantus. However, there are substantial differences between diabetic cats, and the insulin dose has to be adapted according to the need of the individual cat. If hypoglycemia is noted at any time, the insulin dose should be reduced and another reevaluation scheduled soon

thereafter. Most diabetic cats can be adequately controlled with insulin doses between 0.5 and 3 IU/cat b.i.d. (i.e., usually with less than 1.0 IU/kg b.i.d.). If the insulin requirement increases to 1 IU/kg b.i.d. or more without achieving adequate control, further work-up for any disease causing insulin resistance is indicated.

Diabetic remission may occur in approximately 25% to 50% of cases, usually during the first 3 months of therapy. Therefore, an "extended" treatment goal is to increase the chance of diabetic remission. We do not use a specific remission protocol (meaning to aim for lower glucose targets), because more aggressive insulin treatment is associated with a greater risk of hypoglycemia. However, we always start insulin therapy immediately after diagnosis and aim for good glycemic control. All of our owners are aware of the blood glucose targets mentioned earlier. If those targets are reached and the owner is willing to perform home monitoring of blood glucose, we consider "to push" treatment a bit further to see if diabetic remission is possible (see details in the sections Home-Monitoring of Blood Glucose, Frequency of Monitoring, and Interpretation of Blood Glucose Curves and Adjustment of Insulin Doses). The target for the glucose nadir, however, is not altered (i.e., blood glucose concentration should not decrease to less than 80 to 120 mg/dL [4.5 to 6.7 mmol/L]). If remission occurs unnoticed and the administration of insulin is not discontinued, serious hypoglycemia may result.

Oral Hypoglycemic Agents and Non-Insulin Injectables

In humans with newly-diagnosed type 2 diabetes, initial therapeutic measures consist of lifestyle interventions and prescription of an oral hypoglycemic agent. According to the latest position statement of the American Diabetes Association and the European Association for the Study of Diabetes, metformin is the initial drug of choice. If the glycemic target is not reached after approximately 3 months of metformin therapy, another antidiabetic drug should be added. This may be a sulfonylurea, thiazolidinedione, dipeptidyl peptidase-4 (DPP-4) inhibitor, GLP-1 receptor agonist, or insulin. In newly-diagnosed human patients with severe diabetic symptoms and severe hyperglycemia (blood glucose > 300 to 350 mg/dL, 16.7 to 19.4 mmol/L), insulin therapy should be started immediately (Inzucchi et al, 2012). In short, this means that if β-cell function has deteriorated beyond the capacity of oral agents to provide adequate glycemic control, the introduction of insulin should not be delayed (Bailey and Krentz, 2010). It is currently assumed that the majority of diabetic cats suffer a type 2-like diabetes, and therefore, oral hypoglycemic drugs and non-insulin injectables may theoretically be of use. However, those classes have not gained wide popularity, certainly due to two main reasons. First, it may be as difficult (or even more difficult) for a cat owner to give life-long oral medication as to inject insulin. Secondly, for those drugs investigated in the cat, efficacy has been poor or moderate at best. Diabetic cats usually have symptoms of severe hyperglycemia and insulin secretion is low. As in humans with severe disease, oral drugs and non-insulin injectables are usually unable to combat the profound metabolic derangements. Immediate and effective treatment should be initiated with the aim of preserving the remaining β-cell mass and reversing the effects of glucotoxicity on β-cell function. We consider insulin treatment superior to any other currently available antidiabetic drug to increase the chance of diabetic remission. Insulin therapy is therefore highly recommended to owners of cats with newly diagnosed diabetes. Oral drugs and non-insulin injectables (e.g., the GLP-1 agonists) may play a role in cats with mild forms of diabetes or as add-on treatment. The latter are also used when the owner absolutely refuses to inject insulin or is unable to do so.

The currently available oral agents and non-insulin injectables can be divided by their mechanism of action into several groups: insulin secretagogues (sulfonylureas, glinides), insulin sensitizers with predominant action on the liver (metformin), insulin sensitizers with predominant action in peripheral insulin-sensitive tissues (glitazones), carbohydrate absorption inhibitors (α-glucosidase inhibitors), incretin-related therapies (DPP-4 inhibitors, GLP-1 agonists), and others/novel agents with less clear mechanisms (Buse et al, 2011; Table 7-5). Not all agents are available in all countries, and the same drug may be named differently in different countries.

Sulfonylureas

Sulfonylureas were introduced into human medicine in the 1950s and are the oldest oral hypoglycemic agents. Early sulfonylureas are referred to as "first generation" and include tolbutamide, carbutamide, acetohexamide, tolazamide, and chlorpropamide. They have largely been replaced by the more potent "second generation" sulfonylureas, such as glipizide, glyburide (glibenclamide), gliclazide, and glimepiride. They act directly on the β-cell to induce insulin secretion; they do so by binding to the cytosolic surface of the sulfonylurea receptor, which causes closure of ATP-sensitive potassium channels, followed by depolarization of the plasma membrane, opening of calcium channels, and exocytosis of insulin

TABLE 7-5 **CLASSES OF ORAL HYPOGLYCEMIC AGENTS AND NON-INSULIN INJECTABLES AND THEIR MAIN MODES OF ACTION**

CLASS OF ANTIDIABETIC DRUG WITH EXAMPLES	MAIN MODE OF ACTION	PREDOMINANT SITE OF ACTION
Sulfonylureas (glipizide, glyburide/glibenclamide, gliclazide, glimepiride)	Stimulate insulin secretion	β-cells
Glinides/meglitinides (repaglinide, nateglinide)	Stimulate insulin secretion (faster onset and shorter duration of action than sulfonylureas)	β-cells
Biguanide (metformin)	Decrease of hepatic gluconeogenesis and glycogenolysis, increase of glucose-uptake	Liver (muscle)
Glitazones/thiazolidinediones (pioglitazone, rosiglitazone)	Increase insulin sensitivity	Adipose tissue, muscle, (liver)
α-glucosidase inhibitors (acarbose, miglitol, voglibose)	Slow digestion of carbohydrate	Small intestine
GLP-1 receptor agonists (exenatide, liraglutide, albiglutide) DPP-4 inhibitors/gliptins (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin)	Enhance glucose-dependent insulin secretion (see also Table 7-10)	β-cells

DPP-4, Dipeptidyl peptidase-4; *GLP-1,* glucagon-like peptide-1.

(Bailey and Krentz, 2010). Sulfonylureas can only exert their effect if there is a sufficient reserve of β-cells function left, and they usually become ineffective as β-cell function declines during the progression of the diabetic disease. They are contraindicated in individuals with an absolute insulin deficiency. Sulfonylureas can stimulate insulin release even if blood glucose concentrations are low (< 90 mg/dL, 5 mmol/L), rendering hypoglycemia the most serious adverse effect. Another negative effect of sulfonylurea therapy is weight gain.

Glipizide is the drug in this class most often used in cats and which has been studied best (Nelson et al, 1993; Feldman et al, 1997). There are no parameters to help the clinician identify cats that will respond to glipizide therapy, and selection of patients therefore relies on assessing the severity of disease. Glipizide should only be used in diabetic cats that are in good physical condition, non-ketotic, have only mild to moderate signs of diabetes, and can be monitored closely. The starting dose of glipizide is 2.5 mg/cat b.i.d. in conjunction with a meal. The dose is increased to 5 mg/cat b.i.d. after 2 weeks provided that no adverse effects have occurred and hyperglycemia is still present. The cat should be reevaluated after another 1 to 2 weeks and at regular intervals thereafter. Therapy is continued as long as the drug provides good glycemic control, i.e., resolution of clinical signs, stable body weight, blood glucose concentrations between 180 to 270 mg/dL (10-15 mmol/L) and 80 to 140 mg/dL (4.5-7.8 mmol/L). The dose should be reduced or discontinued if normoglycemia or hypoglycemia occurs, and the cat should be reevaluated after a few days. If hyperglycemia is again present, glipizide at a lower dose should be reintroduced. Glipizide should be discontinued and insulin therapy started when clinical signs and hyperglycemia are not under control or worsen after a few weeks of treatment or ketoacidosis develops. The dose of glipizide should not be increased above 5 mg/cat b.i.d. Adverse effects (besides hypoglycemia) occur in approximately 15% of cats and include anorexia, vomiting, increased liver enzymes, and increased bilirubin with icterus. Please see Box 7-4 for recommendations in case those adverse effects occur. One should be aware that glipizide is only effective in approximately 30% of cases. In some of them, glipizide becomes ineffective after a few weeks to months; in others, good glycemic control can be maintained for a long period (years). Glipizide may have negative effects on islets and may accelerate β-cell loss. Under experimental conditions, increased amyloid deposition has been found in islets of cats treated with glipizide compared to cats treated with insulin; this is most likely due to the stimulatory effect of glipizide on both insulin and amylin secretion (Hoenig et al, 2000b). This finding is comparable to studies using human cell cultures, in which sulfonylureas lead to increased β-cell apoptosis (Maedler et al, 2005). One study investigated the efficacy of transdermal glipizide; unfortunately absorption was low and inconsistent (Bennet et al, 2005).

BOX 7-4 Adverse Reactions to Glipizide Treatment in Diabetic Cats

Adverse Reaction	Recommendation
Vomiting within 1 hour of administration	Vomiting usually subsides after 2 to 5 days of glipizide therapy; decrease dose or frequency of administration if vomiting is severe; discontinue if vomiting persists longer than 1 week.
Increased serum hepatic enzyme activities	Continue treatment and monitor enzymes every 1 to 2 weeks initially; discontinue glipizide if cat becomes ill (lethargy, inappetence, vomiting) or the alanine aminotransferase activity exceeds 500 IU/L.
Icterus	Discontinue glipizide treatment; reinstitute glipizide therapy at lower dose and frequency of administration once icterus has resolved (usually within 2 weeks); discontinue treatment permanently if icterus recurs.
Hypoglycemia	Discontinue glipizide treatment; recheck blood glucose concentration in 1 week; reinstitute glipizide therapy at lower dose or frequency of administration if hyperglycemia recurs.

There is very little to no experience with other sulfonylureas in diabetic cats. Glyburide (glibenclamide) has a longer duration of action than glipizide and may be suitable for once daily use in some cats. Initial dose is 0.625 mg/cat b.i.d., which may be increased to 1.25 mg/cat b.i.d., if no effect is seen. Guidelines and adverse effects are similar to those described for glipizide. Glimepiride is the most recently developed sulfonylurea for once daily use in humans. So far, it has been investigated only in healthy cats, in which a significant glucose lowering effect was demonstrated (Mori et al, 2009b).

Because sulfonylureas (e.g., glipizide) do not offer any medical advantage over insulin, we only use them if owners are unable or unwilling to inject insulin. During the following weeks, confidence and willingness of owners often increase and a transition to insulin will eventually be possible.

Glinides/Meglinides

Glinides/meglinides are insulin secretagogues, which also bind to the sulfonylurea receptors, but on a different site from sulfonylureas. They induce a prompt, albeit short-lived insulin secretion and are specifically designed to counteract postprandial hyperglycemia. As such, they are also termed *short-acting prandial insulin releasers.* Adverse effects include hypoglycemia and weight gain; severity of both, however, is less than with sulfonylureas (Bailey and Krentz, 2010). Recently, nateglinide (one of the two members of this class) was evaluated in healthy cats. It induced a more rapid and more pronounced increase in insulin secretion than the sulfonylurea glimepiride, resulting in an earlier decrease in blood glucose concentrations (Mori et al, 2009b). There are no reports on their use in diabetic cats, and because cats have unique nutritional characteristics (see Dietary Management), they may not be helpful for glycemic control.

Biguanides

Metformin is the only drug of the biguanide class in most countries. According to the guidelines for the treatment of humans with type 2 diabetes, metformin should be considered as first line medical therapy, provided that there are no contraindications (Inzucchi et al, 2012). Its mechanisms of action are complex and not fully understood. Some of the actions are achieved through enhanced insulin sensitivity, whereas others are independent of insulin, including activation of adenosine monophosphate-activated protein kinase (AMPK) (Bailey and Davies, 2011). The primary site of action is the liver, where it reduces gluconeogenesis and glycogenolysis. Metformin also enhances glucose uptake and glycogenesis in skeletal muscle and promotes glycogen synthesis. The glucose-lowering effect requires the presence of at least some circulating insulin, and therefore metformin is ineffective in patients with complete lack of insulin. Metformin does not stimulate insulin

release, and although it reduces hepatic glucose production, the risk of hypoglycemia is minimal. Weight gain is also not a relevant adverse effect. The main adverse effects in humans are gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal discomfort, diarrhea), and they are usually dose-related and may be reduced in most patients by dose-titration or switching to a slow-release formula. There are various contraindications, such as impaired renal function, cardiac or respiratory insufficiency, liver disease, and others. Metformin may also reduce vitamin B_{12} absorption (Bailey and Krentz, 2010; Bailey and Davies, 2011). The most frightening and serious potential adverse effect is lactic acidosis. An increase in blood lactate concentration is a consequence of the effect of metformin to inhibit hepatic gluconeogenesis, for which lactate is an important substrate. Lactic acidosis, however, is a rare event and mostly associated with the use of metformin in patients with comorbidities and risk factors (e.g., renal insufficiency) (Krentz and Nattrass, 2003; Renda et al, 2013). So far only very few studies have been performed in cats. Doses suggested to be necessary to reach plasma concentrations known to be effective in human diabetics varied between 2 mg/kg b.i.d. and 50 mg/cat b.i.d. (Michels et al, 1999; Nelson et al, 2004). Unfortunately, results achieved in a small number of diabetic cats are not encouraging, because only one of five cats with diabetes responded to treatment. Clinical signs improved 3 weeks after the metformin dose had been increased to 50 mg/cat b.i.d. (from 10 mg/cat s.i.d., 10 mg/cat b.i.d., 25 mg/cat b.i.d.). Three diabetic cats failed to respond and one diabetic cat died unexpectedly some days after initiating therapy. The responder was the only diabetic cat that had detectable insulin concentrations prior to treatment, supporting the concept that some circulating insulin has to be present for metformin to be effective (Nelson et al, 2004).

Glitazones

Glitazones are also known as *thiazolidinediones (TZDs).* Most of their antidiabetic effect is achieved through stimulation of a nuclear receptor, the peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ is highly expressed in adipose tissue and to a lesser extent in muscle and liver. Stimulation results in differentiation of preadipocytes into small, insulin-sensitive adipocytes that take up fatty acids and reduce their availability for gluconeogenesis. TZDs also increase insulin-mediated glucose uptake ("insulin sensitizer") into skeletal muscle and adipose tissue, reduce the production of several proinflammatory cytokines (e.g., TNFα) and increase the production of adiponectin in adipose tissue. They may also be of benefit in early stages of the disease and may slow the progression of β-cell destruction. TZDs, like metformin, require the presence of some circulating insulin to be effective; it may take 2 to 4 months until the full effect is seen. They do not stimulate insulin secretion and do not cause hypoglycemia. They are often taken in combination with other antidiabetic drugs (e.g., metformin) to achieve an additive effect, but they may also be used as monotherapy. Adverse effects include weight gain due to fluid retention and accumulation of subcutaneous fat; they may be associated with an increased risk of heart failure and bone fractures (Bailey and Krentz, 2010; Bailey and Davies, 2011; Buse et al, 2011). So far, no studies describe the use of TZDs in cats with diabetes. The potential for this drug for the treatment of diabetic cats is currently unknown. Healthy cats had significantly lower cholesterol, triglyceride, and leptin concentrations after 6 weeks of darglitazone treatment (2 mg/kg s.i.d., orally) compared with control cats. A significant decrease in the area under the curve for NEFAs, glucose, and insulin during an IVGTT was demonstrated; the latter suggested an increase in insulin sensitivity induced by the drug (Hoenig and Ferguson, 2003). Recently, the pharmacokinetics of pioglitazone, another member of the TZD class, was evaluated in healthy cats. It was suggested that 1 to 3 mg/kg of pioglitazone would be an appropriate oral dose for further studies on its efficacy (Clark et al, 2011).

Alpha-Glucosidase Inhibitors

Drugs of this class are competitive inhibitors of α-glucosidase enzymes in the brush border of enterocytes, lining the intestinal villi. Thereby, they prevent the final step of carbohydrate digestion (i.e., cleavage of disaccharides and oligosaccharides into monosaccharides). As a result, glucose absorption is delayed. It is not inhibited per se but moved distally in the gastrointestinal tract. These drugs can only be effective in the presence of a substantial amount of complex carbohydrate and when given with a meal. The main adverse effects are gastrointestinal signs (e.g., abdominal discomfort, flatulence, and diarrhea), which often limit their use in humans. In humans, they may be used as monotherapy in patients with postprandial hyperglycemia but only slightly increased fasting hyperglycemia. More often, however, they are considered as additive therapy with other antidiabetic drugs (Bailey and Krentz, 2010; Bailey and Davies, 2011). In cats, α-glucosidase inhibitors may be useful in cases in which a high-carbohydrate diet is fed. In diabetic cats, the α-glucosidase inhibitor acarbose (12.5 mg/cat b.i.d. with a meal) had no apparent positive effect when given with a low-carbohydrate diet (Mazzaferro et al, 2003). This observation is consistent with the results of a study comparing the effects of acarbose in healthy cats fed low- and high-carbohydrate diets. Cats on a high-carbohydrate diet had significantly lower blood glucose concentrations when acarbose was added, although the same glucose-lowering effect was seen with the low-carbohydrate diet. The acarbose dose was 25 mg/cat s.i.d. for cats fed once daily, and 25 mg/cat b.i.d. if fed several meals (Singh et al, 2006; Rand, 2012; Palm and Feldman, 2013). As in humans, gastrointestinal side effects may occur, the severity of which may be reduced by slow dose titration. In diabetic cats fed low-carbohydrate diets, acarbose is of no or negligible use. Acarbose has been suggested for diabetic cats in which a low-carbohydrate–high-protein diet may not be appropriate (e.g., in cats with concurrent renal failure). It should be noted, however, that acarbose is considered contraindicated in humans with impaired renal function (Yale, 2005; Tschöpe et al, 2013); the issue has not yet been investigated in cats.

Incretin-Related Therapeutics

Incretins are hormones that are released from the gastrointestinal tract during food intake and that potentiate insulin secretion from the β-cells. GIP and GLP-1 are the two currently known incretin hormones. GIP is ineffective in diabetic individuals, whereas GLP-1 retains its stimulatory effect provided that there is still an adequate mass of β-cells present. It also has beneficial effects on glucagon, gastric emptying, and satiety. GLP-1 is mainly produced in the L-cells in the intestinal tract. In the cat, the highest density of L-cells was recently shown to be in the ileum (Gilor et al, 2013). Native GLP-1 is quickly degraded by the enzyme DPP-4, which has led to the development of GLP-1 agonists with resistance to degradation and to inhibitors of DPP-4 activity (Mudaliar and Henry, 2012). Although both classes improve glycemic control, various differences exist between them. From a practical standpoint, a major difference is the route of application: GLP-1 agonists have to be injected subcutaneously, whereas DPP-4 inhibitors are oral agents. For both GLP-1 agonists and DPP-4 inhibitors, the risk of hypoglycemia

TABLE 7-6 COMPARISON OF GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS

	GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS	DIPEPTIDYL PEPTIDASE-4 INHIBITORS
Administration	Subcutaneous injection	Orally
Glucose-dependent insulin secretion	Enhanced	Enhanced
Glucose-dependent glucagon secretion	Reduced	Reduced
Postprandial hyperglycemia	Reduced	Reduced
Risk of hypoglycemia	Low	Low
Gastric emptying	Decelerated	No effect
Appetite	Suppressed	No effect
Satiety	Induced	No effect
Body weight	Reduced	Neutral
Main adverse effects	Nausea, vomiting	Headache, nasopharyngitis, urinary tract infection

From Reusch CE, Padrutt I: New incretin hormonal therapies in humans relevant to diabetic cats, *Vet Clin North Am Small Anim Pract* 43:417, 2013 (with permission).

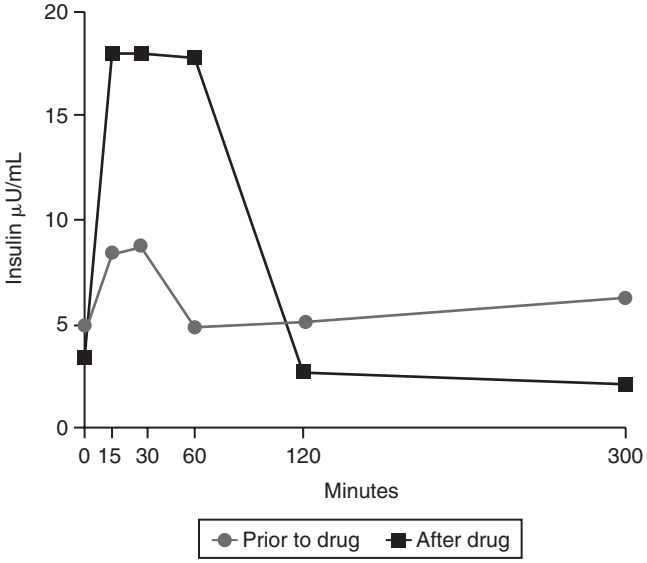

FIGURE 7-16 Insulin secretion before and 5 weeks after once weekly subcutaneous injection of exenatide long-acting (Bydureon). Samples for insulin measurement were taken before and 15, 30, 60, 120, and 300 minutes after feeding a test meal. Results are mean values of three healthy cats. *Prior to drug,* Insulin secretion before the start of the study. *After drug,* Insulin secretion after weekly administration of 200 µg/kg exenatide long-acting for 5 weeks. (From Padrutt I, et al.: Comparison of the GLP-1 analogues exenatide short-acting, exenatide long-acting and the DPP-4 inhibitor sitagliptin to increase insulin secretion in healthy cats, *J Vet Int Med* 26:1520, abstract, 2012.)

is low (Reusch and Padrutt, 2013; Table 7-6). In humans with type 2 diabetes, incretin based therapy is currently used as monotherapy, as well as in combination with other antidiabetic drugs. In the rat and mouse, it has been shown that GLP-1 analogues preserve β-cell mass by inducing β-cell proliferation. There is hope that the same may be true for humans, because this would then be of great benefit to slow progression of the diabetic disease (Rutti et al, 2012). The same would be of course true for the cat.

GLP-1 agonists and DPP-4 inhibitors have thus far been investigated only in healthy cats. The GLP-1 agonist exenatide was shown to potentiate insulin secretion in association with a glucose load, similar to its effect in other species (Gilor et al, 2011). In a dose escalation study, the application of 0.2, 0.5, 1.0, and 2.0 µg/kg exenatide b.i.d. for 5 days resulted in pronounced insulin increase (area under the curve after a meal-response test) of 320%, 364%, 547%, and 198%. Exenatide is also available as long-acting or extended-release preparation, which allows less frequent application (once per week instead of twice daily). Once weekly injection of exenatide long-acting (200 µg/kg) for 5 weeks, resulted in a very efficient increase of meal-induced insulin secretion (Fig. 7-16). The application of the DPP-4 inhibitor sitagliptin in a dose-escalation manner (1, 3, 5, and 10 mg/kg s.i.d. for 5 days) resulted in a less pronounced increase of insulin (43%, 101%, 70%, and 56%). Transient gastrointestinal side effects were seen with all three drugs; however, well-being and appetite were unaffected (Padrutt et al, 2012; Reusch and Padrutt, 2013). Clinical studies in diabetic cats are under way, although the currently high costs of the drugs may be prohibitive for the routine use in practice.

Other Therapies

Chromium is an essential trace element, required for normal glucose metabolism. It is assumed that it may modulate insulin signaling; its precise mode of action, however, is unclear. Trivalent (3+) chromium is found in a wide range of foods and is available as an inexpensive nutritional supplement. Chromium chloride, chromium nicotinate, and chromium picolinate are formulations of trivalent chromium; the absorption of the latter seems to be the most consistent. There is controversy as to whether chromium supplementation should be routinely recommended in diabetic humans without documented deficiency. Some studies have found evidence in favor, others against a beneficial effect (Wang and Cefalu, 2010). In cats, the effect of chromium was so far investigated only in healthy animals and results also differ. In one study, using 100 µg chromium picolinate for 6 weeks, no effect on glucose tolerance was found (Cohn et al, 1999); in another study, a small, but significant improvement in glucose tolerance was seen after chromium picolinate was supplemented for 6 weeks at mean concentrations of 22.9 µg and 44.9 µg (Appleton et al, 2002). Adverse effects were not identified in any of the studies. It is not known if diabetic cats with adequate dietary intake would benefit from additional chromium supplementation.

Vanadium is another trace element, which does have insulin-mimetic properties in liver, skeletal muscle, and adipose tissue; most likely it plays an activating role in the insulin signaling cascade. The effects are similar, regardless of the type of vanadium salts used. Several clinical trials in human diabetics have documented improvement in glycemic control; there is, however, a high incidence of gastrointestinal adverse effects (Smith et al, 2008; Clark et al, 2014). There is very little experience with vanadium supplementation in diabetic cats. Cats treated with insulin (PZI) and oral vanadium dipicolinate (45 mg orally, s.i.d.) had a slightly better glycemic control than cats treated with insulin alone. Adverse effects included anorexia and vomiting (Fondacaro et al, 1999). Further studies are needed to define the role of chromium and

vanadium supplementation in diabetic cats. So far, no dose recommendation can be made due to the lack of dose finding studies. See Herbs, Supplements, and Vitamins in Chapter 6 for a discussion on further "alternative" therapies.

Oral hypoglycemic agents and non-insulin injectables are an area of intensive research in human medicine, and many new drugs have recently been developed. Amongst them are amylin analogues (pramlintide), dopamine agonists (bromocriptine), and sodium-glucose-transporter-2 inhibitors. None of them have been studied in cats so far. Many more will come, and the big challenge will be to critically evaluate them in a sufficient number of diabetic cats.

Dietary Management

Diet is an important component of the treatment plan. The goal of dietary therapy is to provide a nutritionally complete and palatable food that is readily consumed. Regular eating is of particular importance in the diabetic cat, because lack of food intake may lead to hypoglycemia. In addition, the diet should provide day-to-day consistency with regard to composition, ingredients, and calories so that an optimal body condition can be achieved and maintained. The diet should also reduce postprandial hyperglycemia and minimized fluctuations in blood glucose. Choosing an appropriate diet will also increase the chance of diabetic remission.

Obesity

Obesity is an important risk factor for the development of diabetes and the prevalence of both obesity and diabetes is increasing. Obesity is the result of excessive caloric intake, decreased energy expenditure, or both. Neutering and physical inactivity (indoor confinement) lead to a reduction in energy expenditure. Unfortunately, those events are often combined with feeding highly palatable, energy-dense diets in high amounts. Other factors, such as genetic background, epigenetic modulation of gene expression, and the nature of the environment may also contribute (Zoran and Buffington, 2011).

There is some debate on which macronutrients (fat or carbohydrates) play the most important role in the development of obesity. Recent studies showed that diets high in fat result in weight gain and increase in body fat when fed ad libitum (Nguyen 2004; Backus et al, 2007). Body fat increased with increasing dietary fat and an obesity-promoting effect was seen when dietary fat exceeded 25% of metabolizable energy (ME). Because dietary fat was exchanged for carbohydrates, those diets low in fat were high in carbohydrates (and vice versa), providing evidence that diets high in fat pose a greater risk for obesity than diets high in carbohydrates (Backus et al, 2007; Laflamme, 2010). However, consumption of carbohydrates in excess of energy needs will also contribute to obesity, meaning that any excess of calories poses a risk for obesity (Laflamme, 2010). Cats are strict carnivores and need larger amounts of dietary protein than dogs and humans. Although it is the restriction of calories that ultimately leads to weight loss, it is important to minimize loss of lean body mass. Therefore, a weight-loss diet should be calorie-restricted but provide an adequate amount of protein. The minimum daily protein requirement for an adult cat was recently reported to be at least 5.2 g/kg body weight per day. Dietary fiber is a helpful component of weight loss diets. It provides little dietary energy and thereby reduces the caloric density of the diet, and it also has a satiety effect (Laflamme, 2012; Laflamme and Hannah, 2013).

Dietary Carbohydrate and Protein

Several of the commonly manufactured cat foods (in particular dry foods) contain high amounts of carbohydrates (up to 50% of ME). It has been debated whether long-term feeding of those diets contributes to the development of diabetes in cats. The reason behind those debates is the fact that the natural diet of cats in the wild includes mice and birds and is low in carbohydrates and that the feline carbohydrate metabolism has some specifics. For instance, cats have low amylase activity in saliva and the small intestinal tract, and their liver lacks glucokinase, which is an enzyme responsible for phosphorylation of glucose for subsequent oxidation or storage. Glucokinase operates when the liver receives large amounts of glucose from the portal vein. Other glycolytic enzymes, such as hexokinase (a constitutive enzyme), however, were found to be present in even higher concentrations than in the liver of dogs (Washizu et al, 1999; Tanaka et al, 2005). Cats have a rather limited capacity to metabolize simple sugars, and experimental diets containing up to 40% of glucose and sucrose resulted in hyperglycemia and glucosuria (Kienzle, 1994). After eating a glucose enriched meal, healthy cats reveal significant higher blood glucose concentrations than dogs with a later glucose peak and a later return to baseline. More "physiological" dietary studies used different levels of starch instead of adding simple sugars. Using a high-starch diet (43% ME), blood glucose was significantly higher compared to baseline after 11 hours and remained significantly elevated until the end of the trial (19 hours after the meal) in cats; in dogs, blood glucose increased only minimally. After feeding a low or moderate starch diet (12% and 30% ME), glucose concentrations did not increase in both species (Hewson-Hughes et al, 2011a; 2011b). Another study confirmed the finding that cats may have a long postprandial increase in blood glucose concentration. Hyperglycemia, albeit mild, was already seen after feeding a diet with moderate carbohydrate content (25% of ME). Mean baseline glucose concentration was 90 mg/dL (5 mmol/L) and increased to a mean of 130 mg/dL (7.2 mmol/L) after feeding. The median time until blood glucose reached its peak was 6 hours after feeding, and the median time until glucose returned to baseline was 12.2 hours. Insulin concentrations returned to baseline after a median of 12.3 hours (Farrow et al, 2012). Interestingly, the use of a moderate starch diet lead to a postprandial glucose increase in one of the studies, whereas no increase was seen in the other study (Hewson-Hughes et al, 2011b; Farrow et al, 2012). It is possible that the differences are due to the use of different carbohydrate sources in the diets.

De-Oliveira, et al., (2008) fed diets containing 35% of starch from six different carbohydrate sources. Digestibility of the various carbohydrates varied slightly, but was generally very high. The time until the peak blood glucose was reached was quite different between the diets and ranged between 2.5 and 7.2 hours. Interestingly, the overall maximum blood glucose concentration was only 93.3 mg/dL (5.2 mmol/L) (i.e., none of the cats had blood glucose concentrations above the normal range). The highest blood glucose was seen when corn was used as carbohydrate source, followed by brewers rice, and the lowest was with lentil and cassava flour. From the studies mentioned, one may conclude the following: healthy cats seem to be able to digest carbohydrate if properly processed; blood glucose and insulin concentrations increase after dietary carbohydrate intake, the extent of which probably correlates with the carbohydrate concentration and carbohydrate source; the increase of blood glucose, if present, is usually mild, and it is unclear if this slight increase has any negative impact. Currently, there are no studies showing that consumption of high dietary carbohydrates causes diabetes mellitus in cats. It is more

likely that excess intake of those diets leads to obesity, which in turn is a risk factor. Other factors associated with the change in the lifestyle of cats also play a role. Slingerland, et al., (2009) showed that indoor confinement and physical inactivity was significantly correlated with the development of diabetes, whereas the percentage of dry food (high in carbohydrates) was not.

The topic of diet is less controversial in cats with overt diabetes and there is current agreement that a high-protein–low-carbohydrate diet should be fed (Laflamme, 2010; Rucinsky et al, 2010; Zoran and Rand, 2013). High-fiber diets are no longer recommended as diets of first choice in diabetic cats, because they usually do not have a low carbohydrate content. They may, however, be used if cats do not tolerate high-protein–low-carbohydrate diets or if weight loss is insufficient. It should be noted that the current dietary recommendation is based on a relatively small number of clinical studies (Frank et al, 2001; Mazzaferro et al, 2003; Bennett et al, 2006). The most comprehensive study compared a moderate carbohydrate/high-fiber diet (26% carbohydrate [CHO] ME) and a low carbohydrate/low fiber diet (12% CHO ME) randomly assigned to cats with diabetes. After 4 months, significantly more cats fed the low carbohydrate diet were in diabetic remission compared with cats fed the moderate carbohydrate diet (68% versus 41%); of the cats still requiring insulin, more cats on the low carbohydrate diet were well regulated (40% versus 26%) (Bennett et al, 2006). The positive effect on glycemic control occurs before there is apparent loss of body weight. The exact mechanisms involved remain to be investigated (e.g., if low carbohydrate or high protein is the key factor and what roles the different sources of proteins and carbohydrates play).

Current recommendations state that the protein content in a diet for diabetic cats should be more than 40% to 45% ME and the carbohydrate content should be less than 12% to 15% ME, or as low as the cat will eat (Rucinsky et al, 2010; Zoran and Rand, 2013). No clear statements are made with regard to fat content. It has been shown that healthy cats may tolerate high amounts of fat (up to 66% ME) well without negative impact on plasma lipid concentrations (Butterwick et al, 2012). In diabetic cats, however, it seems reasonable to avoid high fat diets (e.g., growth diets), because they may be associated with further weight gain and possibly with increased risk of pancreatitis. Canned food has some advantages over dry food, such as a lower calorie density (the cat can eat more for the same caloric intake), and usually a lower carbohydrate content and provision of additional water, which increases hydration as well as satiety (Rucinsky et al, 2010; Zoran and Rand, 2013). Many diets (in particular canned diets) fulfill the aforementioned criteria. Most premium pet food companies offer diets specifically designed for diabetic cats (Table 7-7). We routinely prescribe canned food with high protein and very low carbohydrate content to the owners of diabetic cats. If palatability is a problem with our first choice diet, we switch to another diet with comparable characteristics. In cats in which diabetic remission is achieved after some time and insulin therapy is discontinued, we recommend that the high-protein–low-carbohydrate diet is fed life-long. Similarly, in cats with prediabetes, weight reduction and feeding a high-protein–low-carbohydrate diet is recommended.

Calculation of Energy Requirement and Feeding Schedule

Energy requirement differs between individuals, and therefore, guidelines should only be used as a rough estimate. The maintenance energy requirement of typical sized (4 to 5 kg), neutered indoor cats is 45 to 55 kcal/kg body weight per day. For neutered male cats, the lower number should be used (Zoran and Buffington, 2011). In obese cats, the calculation of energy requirement should be based on ideal body weight. It is, however, possible that this amount is still too high and energy intake must be reduced much further. A reduction of calories in steps of 10% to 15% every few weeks may be necessary. To avoid loss of lean

TABLE 7-7 **APPROXIMATE NUTRIENT CONTENT OF SOME COMMERCIALLY-AVAILABLE DIETS USED FOR DIETARY MANAGEMENT OF DIABETES AND/OR WEIGHT LOSS IN CATS***

	PROTEIN (% ME)	FAT (% ME)	CH (% ME)	FIBER (g/100 kcal ME)	PROTEIN (g/100 kcal ME)
Purina DM (canned)	46.0	47.3	7.7	0.9	13.1
Purina DM (dry)	46.2	38.1	17.9	0.4	13.2
Hill's Prescription Diet m/d (canned)	45.7	40.7	15.6	1.5	13.1
Hill's Prescription Diet m/d (dry)	42.5	40.9	19.0	0.9	12.1
Royal Canin Diabetic DS (wet)	47.2	38.2	16.8	2.2	13.5
Royal Canin Diabetic DS 46 (dry)	45.2	28.6	30.0	1.0	12.9
Hill's Prescription Diet w/d (canned)	39.2	37.9	26.1	2.9	11.2
Hill's Prescription Diet w/d (dry)	39.2	37.9	26.1	2.3	11.2
Hill's Prescription Diet r/d (canned)	41.0	24.3	39.6	4.8	11.7
Hill's Prescription Diet r/d (dry)	40.7	27.9	35.9	4.1	11.6
Purina OM (canned)	51.1	36.8	13.9	1.9	14.6
Purina OM (dry)	53.7	21.7	28.1	2.4	15.3
Royal Canin Obesity Management (wet)	48.5	31.4	22.9	2.8	13.9
Royal Canin Obesity Management (dry)	45.4	26.2	32.5	2.1	13.0

Courtesy of Prof. Annette Liesegang, Institute of Animal Nutrition, Vetsuisse Faculty, Zurich, Switzerland.
*Metabolizable energy (ME) content was determined using the modified Atwater factors on the basis of data provided by the pet food companies. Results are calculated estimates and the total energy in percent may therefore slightly deviate from 100%.

muscle mass, the diet has to meet the minimum daily protein requirement. It is important to set realistic goals and avoid frustration of the owner. Weight should decrease slowly; a loss of 1% per week is considered optimal. Severely overweight cats may never reach optimal body weight; however, a moderate weight loss may improve glycemic control. A small percentage of diabetic cats are underweight. If insulin therapy does not lead to the desired weight gain, calories should be increased in steps of 10% to 15%. Diabetic cats should be weighted once per week, providing that their owners have a precise scale. At each veterinary visit, the notes of the owners should be reviewed, body weight as well as body and muscle scoring should be evaluated, and amounts of calories should be amended if needed. It should be remembered that cats with untreated diabetes lose weight, which is stopped with adequate insulin therapy. Many cats gain some weight with the start of insulin therapy (when calories are not restricted) as the body aims for its original weight. Persistent weight gain, however, should alert the clinician to consider high caloric intake, insulin overdose, or acromegaly as possible causes. Persistent weight loss may be caused by low caloric intake, inadequate insulin therapy, or any concurrent disease (e.g., pancreatitis, pancreatic insufficiency, hyperthyroidism, inflammatory bowel disease, or lymphoma). The best feeding pattern for diabetic cats is unknown at the moment. We currently recommend to offer half of the cat's daily calorie intake at the time of each insulin injection; any leftovers should remain available to the cat until the next meal (Box 7-5).

Modifications in Dietary Therapy

In cats with concurrent disease (e.g., pancreatitis, food allergy, or chronic renal failure) diets designed for diabetes management may not be appropriate. Dietary therapy for the most serious disease should take priority. Please see Modifications in Dietary Therapy in Chapter 6.

BOX 7-5 Recommendations for Dietary Treatment of Cats with Diabetes Mellitus

Dietary Composition
- First choice: High-protein and low-carbohydrate diet (protein > 40 to 45 ME, carbohydrate < 12% to 15% ME)
- Second choice: High-fiber and moderate carbohydrate diet

Type of Food
- First choice: Canned food
- Second choice: Mixture of canned and dry food

Calculation of Quantity
- Energy requirement for an average sized indoor neutered cat is 45 to 55 kcal/kg body weight per day (use lower number for neutered male cats)
- If cat is overweight, aim for loss of 1% of body weight per week
- Adjust daily caloric intake on individual basis
  - Reduce in steps of 10% to 15% if cat is overweight and no weight loss is achieved
  - Increase in steps of 10% to 15% if cat is underweight and no weight gain is achieved during insulin therapy
- Avoid loss of lean body mass by providing adequate amount of protein (5.2 g/kg body weight per day)

Feeding Schedule
- Half of daily caloric intake at time of each insulin injection; any leftover should remain available for the rest of the day or the night

ME, Metabolizable energy.

Exercise

In humans, the positive effect of physical activity on glycemic control is well known. Exercise is associated with improved insulin sensitivity through various mechanisms (e.g., increased postreceptor insulin-signaling, increased GLUT protein, increased delivery of glucose to muscle, and decrease in body fat; Yardley et al, 2010). According to the current recommendations of the American Diabetes Association, adult humans should perform at least 150 min/week of moderate intensity aerobic physical activity with no more than 2 consecutive days without exercise (American Diabetes Association, 2013). In dogs, comparable physical activity can be achieved by daily walks of similar intensity; this kind of therapeutic intervention is limited in the cat. However, so-called environmental enrichment may increase the level of activity and may also have positive psychological effects on the diabetic cat. Enrichment strategies include structured play, use of toys (e.g., wire toys mimicking air-borne prey), food balls, cat trees, play tunnels, and others (Ellis, 2009; Hoyumpa Vogt et al, 2010).

Concurrent Problems

Any concurrent disease (inflammatory, infectious, metabolic, or neoplastic) can cause insulin resistance and can have a negative impact on the management of diabetes. Insulin resistance may range from mild to severe or may fluctuate over time. A thorough evaluation of newly-diagnosed diabetic cats is of great importance, and any concurrent problem should be addressed appropriately. Similarly, glucocorticoids and progestagens have a negative influence on insulin sensitivity, and their administration should be stopped immediately. If a concurrent disease requires immunomodulatory medication, alternative drugs should be used if possible (e.g., Ciclosporin). If glucocorticoids are absolutely required, the dose should be kept as low as possible and administration as infrequent as possible. Insulin dose will be higher in those cases and need to be adjusted whenever the glucocorticoid dose is changed. Successful treatment of concurrent problems (e.g., oral care, eradication of urinary tract infection) and/or cessation of diabetogenic drugs oftentimes result in improved glycemic control and improve the chance of diabetic remission. Some diseases, such as chronic renal failure and chronic pancreatitis, cannot be cured and require long-term management. Treatment of diabetes in those situations is often very difficult because there may be substantial fluctuations in insulin sensitivity. Owners should be made aware that treatment may be very challenging and more frequent monitoring and dose amendments than in the usual diabetic cat may be required. The presence of hyperadrenocorticism and acromegaly is oftentimes not suspected until large doses of insulin are required (see Concurrent Disorders Causing Insulin Resistance and Drug-Induced Diabetes in this chapter and Concurrent Disorders Causing Insulin Resistance in Chapter 6.

TECHNIQUES FOR MONITORING DIABETIC CONTROL

The primary goals of therapy are to eliminate the clinical signs of diabetes while preventing short-term complications (hypoglycemia, DKA). Concurrent problems also need to be controlled, because they may render glycemic control difficult. See Reevaluation and Adjustment of Insulin Dose and Box 7-3 for further details on treatment goals, blood glucose targets, and times of reevaluations. The monitoring techniques are similar for dogs and cats. Different from dogs, however, cats may develop stress hyperglycemia when brought to an unfamiliar environment and/or

manipulated by a veterinarian. Stress hyperglycemia may render the interpretation of blood glucose concentrations and BGCs generated in the hospital difficult. Measurement of blood glucose at home is less stressful or even stress-free when done by experienced owners, and results of home monitoring are usually more reliable than results generated in the hospital.

History and Physical Examination

The most important parameters to assess glycemic control are the clinical signs observed by the owner: the stability of the body weight and the findings during physical examination. Cats, in which the initial clinical signs (e.g., polyuria, polydipsia, polyphagia, lethargy, and/or poor hair coat) have resolved, the body weight stays within the desired range, and physical examination reveals a good clinical condition are usually well controlled. In those cases, measurement of serum fructosamine concentration and generation of BGCs will help to confirm the status of good glycemic control and are useful for the "fine-tuning" of insulin therapy. The measurements also help to determine if diabetic remission has occurred. Persistence or reoccurrence of clinical signs and unwanted weight loss is suggestive of inadequate glycemic control or the presence of another disease. Serum fructosamine and in particular generation of BGCs help to characterize the exact problem and to guide the amendment of therapy. Additional tests may be needed in cases in which history or physical examination suggests the presence of a concurrent disease.

Serum Fructosamine Concentration

Fructosamine is the product of an irreversible reaction between glucose and the amino groups of plasma proteins. Its concentration mainly depends on the blood glucose concentration (e.g., extent and duration of hyperglycemia) and the lifespan of plasma proteins; it is generally assumed that fructosamine reflects the mean blood glucose concentration of the preceding 1 to 2 weeks. The reference ranges differ slightly between laboratories but are usually between approximately 200 and 360 µmol/L. To enable comparison between consecutive measurements, serum samples should always be sent to the same laboratory. Fructosamine is measured in serum using commercially-available test kits adapted to autoanalysis. Shipping should be on cold packs if samples will be in transit for more than 24 hours. Lean cats have lower fructosamine concentrations than normal weight or obese cats, whereas age has no influence. In two older studies, fructosamine did not differ between male and female cats, whereas in the most recent study, fructosamine was higher in male cats (Thoresen and Bredal, 1995; Reusch and Haberer, 2001; Gilor et al, 2010b). In the vast majority of newly diagnosed diabetic cats, fructosamine levels are more than 400 µmol/L and may be as high as 1500 µmol/L. Fructosamine is not affected by short-term increases in blood glucose concentration and thus is usually normal in cats with stress hyperglycemia (Reusch et al, 1993; Lutz et al, 1995; Crenshaw et al, 1996).

However, fructosamine is not a foolproof parameter, and certain aspects need to be considered. In cats with a very recent onset of diabetes or with mild diabetes, serum fructosamine may be in the normal range, rendering the differentiation between stress and diabetic hyperglycemia impossible. In a recent study, two groups of healthy cats were infused with glucose to maintain either a marked or a moderate hyperglycemia (540 mg/dL, 30 mmol/L; or 300 mg/dL, 17 mmol/L) for 42 days. In the group with marked hyperglycemia, it took 3 to 5 days until fructosamine exceeded the upper limit of the reference range; in the group with moderate hyperglycemia, fructosamine concentrations mostly fluctuated just below the upper limit of the reference range (Link and Rand, 2008).

Fructosamine is also influenced by plasma protein concentration and by protein turnover. It has been shown that cats suffering from hypoproteinemia or hyperthyroidism have significantly lower levels of fructosamine than healthy cats (Reusch and Tomsa, 1999; Graham et al, 1999; Reusch and Haberer 2001). It is possible that diabetic cats with concurrent hypoproteinemia or uncontrolled hyperthyroidism may have normal (or even low) fructosamine levels, which would then be misinterpreted as indicative for stress hyperglycemia. In those situations (e.g., cats with concurrent hyperthyroidism or hypoproteinemia), fructosamine should be interpreted only if it is increased, which then indicates diabetes mellitus. There are arguments for and against correction of fructosamine for the serum protein level. Correction, however, may lead to falsely high concentrations and is not recommended. In the majority of situations, fructosamine is a helpful parameter to differentiate between stress- and diabetes-related hyperglycemia.

After initiating insulin therapy, blood glucose concentrations usually start to decrease, which is followed by a decrease in fructosamine after a few days. We consider 50 µmol/L to be the so-called critical difference (i.e., the difference between two consecutive fructosamine measurements has to exceed 50 µmol/L to reflect a change in glycemic control; Reusch, 2013). Another study found a lower critical difference of 33 µmol/L (Link and Rand, 2008). Generally, fructosamine concentrations increase when glycemic control worsens and decrease when glycemic control improves. As mentioned earlier, serum fructosamine concentration is not affected by a short term increase in blood glucose concentration, which may be seen in cats in the hospital. It is also not affected by lack of food intake, which is common in hospitalized cats and often leads to much lower blood glucose concentrations than what is seen with food intake. Routine measurement of fructosamine is therefore helpful to clarify the effects of stress or lack of food intake (e.g., to clarify discrepancies between history and physical examination and blood glucose measurements). Most well-controlled diabetic cats are slightly hyperglycemic for some time during a 24-hour period, and consequently, fructosamine concentrations will not become completely normal during therapy. In cats that achieve diabetic remission, however, fructosamine concentrations decrease into the normal range (Fig. 7-17).

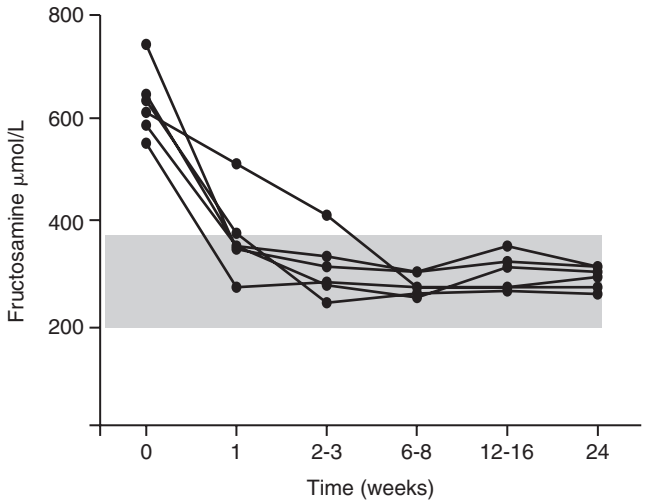

FIGURE 7-17 Serum fructosamine concentrations in six cats with diabetes mellitus experiencing diabetic remission. Remission occurred during the first 12 weeks of therapy, and diabetes of all cats was still in remission after 24 weeks. *0,* Initial presentation; *gray area,* reference range (200 to 340 µmol/L).

As long as fructosamine is elevated (even if only slightly), we do not consider cats to be in diabetic remission. In those cases, insulin therapy is continued under close supervision. Fructosamine concentrations between approximately 350 and 450 µmol/L reflect good glycemic control, concentrations between 450 and 550 µmol/L suggest moderate, and concentrations above 550 to 600 µmol/L suggest poor glycemic control. In the latter situation, fructosamine is not helpful to identify the underlying problem because the various possible reasons for poor regulation (e.g., application error, insulin underdose, too short duration of insulin effect, diseases causing insulin resistance, or Somogyi phenomenon) are associated with high blood glucose concentrations and therefore have the same impact. Generation of one or several BGCs and revision of the owner's injection technique are usually the next steps in those cases. Fructosamine concentrations less than 350 µmol/L suggest diabetic remission, hypoglycemia or concurrent hypoproteinemia, or hyperthyroidism (Reusch, 2010). It is important to note that there are substantial differences in glycation between individuals. In healthy cats in which blood glucose was maintained at 540 mg/dL (30 mmol/L), fructosamine concentrations ranged between 400 and 633 µmol/L when the plateau was reached (Link and Rand, 2008). The study underscores that diabetic cats with similar quality of glycemic regulation may have quite different fructosamine concentrations. The ranges of interpretation listed earlier therefore should only be used as rough guidelines. Fructosamine is useful if followed in individual cats over time; however, it should never be used as the sole indicator of the quality of metabolic control. The parameter is less important than the evaluation of clinical signs and body weight and generation of BGCs.

DKA, dehydration, acidosis, and other unidentified factors may influence fructosamine concentrations. If a diabetic cat is hospitalized for any reason, fructosamine levels measured at the time of admission may be considerably different from concentrations measured a few days later. It is therefore reasonable to repeat the measurement at the time of discharge and to use this concentration as a reference point. See Serum Fructosamine Concentration in Chapter 6 for additional information.

Glycated Hemoglobin Concentration

Glycated hemoglobin is formed by non-enzymatic, irreversible binding of glucose to amino groups of the globin part of the hemoglobin molecule. Its concentration reflects the average blood concentration over the lifespan of the erythrocytes, which is approximately 70 days in the cat. In human diabetics, glycated hemoglobin is one of the cornerstones of glycemic control, and its measurement in regular intervals is strongly recommended (American Diabetes Association, 2013). The matter is somewhat confusing because many different measuring methods are available that measure different species of the molecule. Currently, considerable effort is made in human medicine for an international standardization of glycated hemoglobin measurement (John, 2012). In humans, HBA_{1c} is the component present in largest amounts and results from binding of glucose to the N-terminal amino acid valine of the β-chain of hemoglobin. HBA_1 is a series of glycated variants resulting from the binding of different carbohydrates to valine and includes HBA_{1a} and HBA_{1b}, as well as HBA_{1c}. Total glycated hemoglobin denotes the binding of all carbohydrates at any site of the hemoglobin molecule. High-performance liquid chromatography (HPLC) mainly measures HBA_{1c} as do the newer immunoassays, whereas affinity chromatography methods measure total glycated hemoglobin (Pickup, 2003).

Feline hemoglobin differs considerably from human and canine hemoglobin, which limits the use of some of the human assays. Successful measurement of glycated hemoglobin has been achieved by HPLC and affinity chromatography (Hasegawa et al, 1992; Hoyer-Ott et al, 1995; Elliott et al, 1997; 1999; Haberer and Reusch, 1998; Hoenig and Ferguson, 1999). Glycated hemoglobin was shown to be significantly higher in diabetic cats compared to healthy cats and to cats with stress hyperglycemia. It was also higher in poorly-controlled than in well-controlled diabetic cats. Its concentration decreased significantly after initiating insulin therapy or after improvement of glycemic control respectively. Glycated hemoglobin is measured in ethylenediaminetetraacetic acid (EDTA) whole blood; the molecule is stable at 4° C for at least 1 week. As stability at room temperature differs between assays, the instructions of the laboratory should be followed for shipping. We no longer use glycated hemoglobin mainly because of the limited availability of assays validated for the cat and the lack of advantage over fructosamine, which is very easy to measure. Additionally, glycated hemoglobin in cats is substantially lower than in dogs and humans, and the increase in case of diabetes is less pronounced. Consequently, the difference between well-, moderately-, and poorly-controlled cats is quite small, and the interpretation of results therefore is more difficult.

Urine Glucose Monitoring

Glucose is freely filtered by the glomerulus and reabsorbed in the proximal tubules by the sodium-glucose cotransporter 2 (SGLT2). The reabsorption capacity is limited, and when the blood glucose concentration exceeds the so-called renal threshold (approximately 17 mmol/L, 300 mg/dL in cats), glucose is excreted in the urine. The higher the blood glucose concentration is, the more glucose is found in the urine, which would render the urine test a valuable monitoring tool in theory. However, measurement of urine glucose may be misleading for several reasons: (1) the result does not reflect the actual blood glucose concentration, but is an average over the time of urine accumulation in the bladder; (2) a negative urine test does not differentiate between hypoglycemia, normoglycemia, or mild hyperglycemia; and (3) hydration status and urine concentration may affect the result. It should also be noted that the renal threshold mentioned earlier is only an approximate number. It is known from humans that there are substantial differences between individuals and the threshold may also change within the same individual. Therefore, marked hyperglycemia may exist without glycosuria, or glycosuria may occur with a normal blood glucose concentration (Pickup, 2003; Rave, 2006). Very few studies have investigated the analytical aspects of urine glucose testing in cats. Recently, a commonly used test strip (Bayer Multistix) was compared with a litter additive designed for monitor urine glucose at home (Purina Glucotest). The Multistix inaccurately classified the degree of glycosuria in 24.2 of samples (19% overestimation, 5.2% underestimation). The Glucotest was read immediately after exposure to urine and at different time points thereafter over the course of 8 hours. At the initial reading, the test was inaccurate in 22 % of samples (21% overestimation, 1% underestimation); the inaccuracy decreased to 10% and 3% when the test was read at 30 minutes and 8 hours, respectively (Fletcher et al, 2011).

In summary, numerous biological and analytical factors render urine glucose testing unreliable. In our hospital, we do not adjust insulin dosages based on urine glucose measurements, and we strongly discourage owners from doing so. Owners who are unable to measure blood glucose but still want to do some type of monitoring may be advised to use urine glucose measurements in all urine

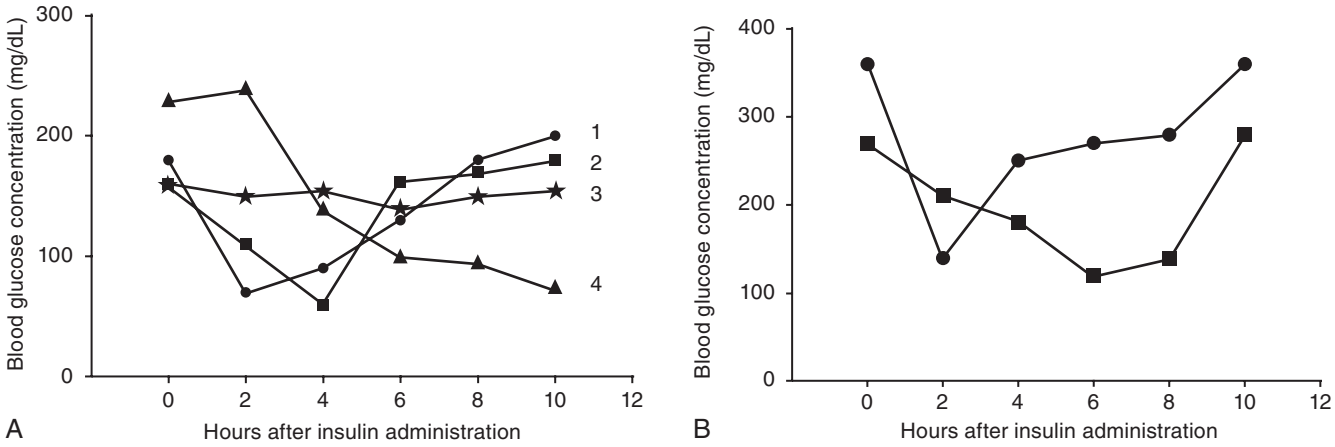

FIGURE 7-18 A, Variable glucose nadirs during blood glucose curves (BGCs) in four diabetic cats treated with insulin glargine (Lantus) between 1 to 2.5 U/cat b.i.d. In cat 1 and 2, the nadirs are 2 and 4 hours, respectively, after insulin administration. Cat 3 does not display an obvious nadir, and in cat 4, the nadir has not been reached during the time of blood glucose measurements (e.g., the nadir is ≥ 10 hours after insulin administration). Insulin glargine has been designed as a peakless insulin for humans. However, in a substantial percentage of cats, a clear peak of action (associated with a clear nadir) is seen during BGCs. Some cats, in particular well-regulated cats, do not show a nadir, and the BGC resembles a flat line as in cat 3. **B,** Two BGCs generated 4 weeks apart from each other in the same cat at home showing different times of glucose nadirs (after 2 and 6 hours respectively). The cat was treated with 1.5 U/cat insulin glargine (Lantus) at both points in time. *0,* Time of insulin administration. To convert mg/dL into mmol/L, multiply blood glucose concentration by 0.056.

samples voided throughout 1 day per week. Replacement of litter by nonabsorbable material (e.g., aquarium gravel) facilitates urine collection. Persistent glycosuria would suggest inadequate glycemic control and the need for thorough evaluation in the hospital. If no glucose is detected in any of the samples, the cat is either very well controlled, is in diabetic remission, or is overdosed with insulin and should be evaluated by a veterinarian. In cats prone to develop DKA, we recommend that the owners check the urine for ketone bodies on a regular basis (e.g., once to twice per week).

Single Blood Glucose Determination

Measurement of a single blood glucose concentration is usually insufficient to assess glycemic control. The exception may be cats with long-standing diabetes in which clinical signs of diabetes mellitus have disappeared, physical examination is unremarkable, and serum fructosamine concentration ranges between 350 and 450 µmol/L. In these cases, the finding of a blood glucose concentration between 180 and 270 mg/dL (10 to 15 mmol/L) around the time of insulin injection is usually consistent with good glycemic control and may render further glucose measurements unnecessary. In cats with more recent onset of diabetes, achievement of diabetic remission is potentially possible and generation of a BGC should be pursued. It is the glucose nadir measured during a BGC that mainly determines if there is room for further (slight) increase in insulin dose. Of note, the time of the glucose nadir varies between cats and also within the same cat (Fig. 7-18). Therefore, determination of a single glucose concentration at the time of the assumed nadir may be misleading.

A single low blood glucose concentration most often is due to insulin overdose, but may also be seen if there is lack of food intake.

Blood Glucose Curve

In addition to evaluation of clinical signs, serial measurement of blood glucose throughout the day (known as *blood glucose curve, BGC*) is the most important monitoring tool for diabetic cats. BGCs are particular important during the initial phases of therapy. During the first weeks to months, insulin doses usually need to be adjusted several times; it is also most often during the first 3 months of therapy that diabetic remission occurs. During long-term management regular, albeit less frequent generation of BGCs is helpful to ensure that the animal is still well-regulated. If clinical signs of diabetes reappear at any time during long-term management, generation of BGCs helps to identify the underlying problem and allows informed dose amendments.

Generation of Blood Glucose Curves in the Hospital

We prefer that owners give insulin and food at home, and then bring the cat to the hospital as soon as possible (within 2 hours) for a BGC. This approach eliminates the effect of lack of food intake on blood glucose levels—at least in those cats that are fed only at the time of insulin administration. When technical difficulties are suspected, owners are asked to bring the cat to the hospital before insulin application and to carry out the entire administration procedure under supervision of a veterinarian or a technician. We generate BGCs by measuring the glucose concentration on average every 2 hours throughout the day until the next insulin administration is due. Shorter intervals (i.e., 1 hour) are chosen in cats with suspected hypoglycemia, and longer intervals (i.e., 3 hours) are sufficient in patients with stable disease. If the glucose nadir is not reached during this time, insulin administration should be delayed and glucose measurements continued. The cat should be handled as carefully as possible and any unnecessary manipulation should be avoided to reduce stress. Blood samples are not obtained by venipuncture but by collecting capillary blood from the ear or the footpad using the same PBGM meter as the owner at home. Usually, the cat can stay in the cage, and when performed by an experienced technician, the procedure is usually well tolerated. With these precautions, we often achieve meaningful measurements (i.e., blood glucose concentrations that match

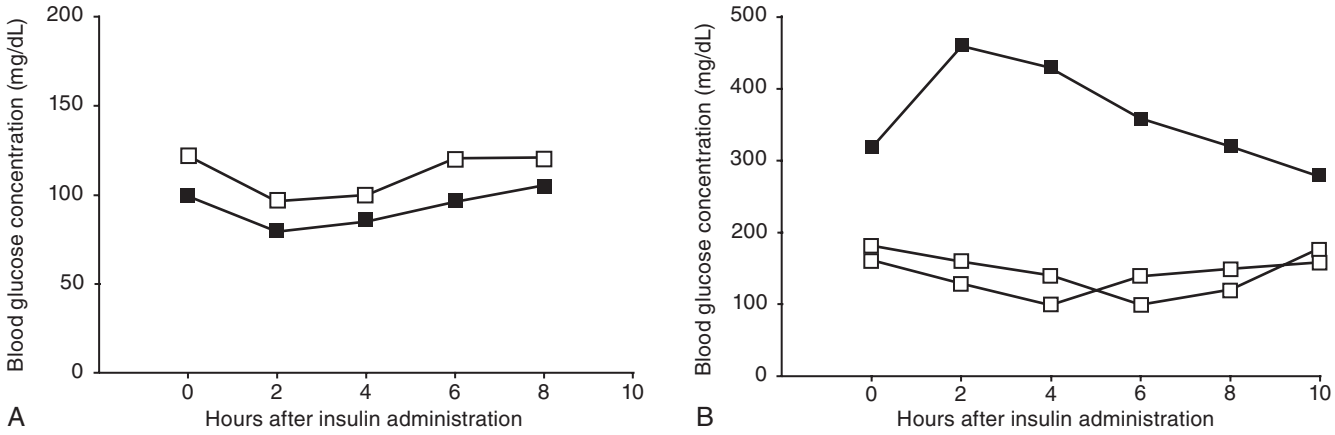

FIGURE 7-19 **A,** Example of a good correlation between blood glucose curves (BGCs) generated in the hospital and at home by the owner. The two curves were generated 3 days apart from each other. The cat (Domestic Short-Hair [DSH], castrated male, 7 kg, 15 years old) received 1 U/cat insulin glargine (Lantus) b.i.d. at both points in time. Clinical signs were well controlled and serum fructosamine concentration was 346 μmol (reference range 200 to 340 μmol/L). *Open squares,* BGC generated at home; *closed squares,* BGC generated in the hospital. **B,** Example of a poor correlation between BGCs generated in the hospital and at home by the owner. The owner generated BGCs at home for 2 consecutive days; another BGC was generated in the hospital 1 week thereafter. The cat (DSH, castrated male, 4.4 kg, 11 years old) received 0.5 U/cat Lente-type insulin (Vetsulin/Caninsulin) b.i.d. at all three points in time. Clinical signs of diabetes were well controlled, and serum fructosamine concentration was 358 μmol/L (reference range 200 to 340 μmol/L). The two home-BGCs show good agreement with each other and support the clinical assessment of good glycemic control. The blood glucose concentrations in the hospital are substantially higher and were attributed to stress. Insulin dose was not changed and the cat continued to do well. *Open squares,* BGCs generated at home; *closed squares,* BGC generated in the hospital. *0,* Time of insulin administration. To convert mg/dL into mmol/L, multiply blood glucose concentration by 0.056.

very well with our clinical impression and the serum fructosamine concentration; Fig. 7-19).

Generally, however, BGCs generated in the hospital are prone to be affected by stress, abnormal housing conditions (small cage compared to free-roaming in the house), and decreased food intake. Cats are particularly sensitive to stress caused by an unfamiliar environment and manipulation by the veterinarian or technician. Consequently, blood glucose concentrations may rise during the BGC and never decrease again while the cat is in the hospital, or glucose levels may be high from the beginning. Blood glucose concentrations in stressed cats in excess of 300 mg/dL (17 mmol/L) are common and may even be higher than 400 mg/dL (22 mmol/L). Stress hyperglycemia should be suspected if the cat is obviously upset or aggressive, although it may also occur in cats appearing calm. The most reliable indicator of stress hyperglycemia is a discrepancy between the clinical impression, body weight, and fructosamine concentration on the one hand and results of the BGC on the other. Lack of food intake has the opposite effect because it may result in low blood glucose concentrations, a situation which is difficult to differentiate from insulin overdose. In addition, BGCs are time-consuming and expensive, and therefore they are often not performed as often as required. It is easy to overlook diabetic remission if blood glucose concentrations are not measured frequently. The veterinarian may also be more reluctant to increase the insulin dose in cats in which BGCs are performed only sporadically, which may hamper achievement of good glycemic control or diabetic remission. Close monitoring of blood glucose is also indicated in diabetic patients with concurrent diseases, which may require frequent adjustments of the insulin dose. See the sections Home Monitoring of Blood Glucose, Frequency of Monitoring, and Interpretation of Blood Glucose Curves and Adjustment of Insulin Doses for more details.

Home Monitoring of Blood Glucose

Treatment success depends largely on the active participation of the owner and on how well he or she is trained for this task by the veterinarian or the technician. The owner should assess the cat for clinical signs of diabetes on a daily basis, and body weight should be measured at least once per week. Home monitoring of blood glucose by the owner was developed approximately 15 years ago and since then has been a routine part of our diabetic treatment and monitoring protocol (Wess and Reusch, 2000). Home monitoring enables frequent blood glucose measurements, and consequently the insulin dose can be amended more often and more precisely. The technique is of particular value in cats because stress hyperglycemia and the potential of diabetic remission renders diabetic monitoring even more challenging than in dogs.

All of our cat owners are introduced to the option of home monitoring of blood glucose, and many of them are willing and able to generate BGCs on a long-term basis (e.g., for several years). Once owners are familiar with the technique, they highly appreciate having more control over the disease. Major points mentioned by owners were that they could monitor blood glucose frequently and were able to assess if changes in the cats well-being are associated with hypo- or hyperglycemia. Owners also appreciate that home BGCs are less stressful for the cat than in-hospital BGCs (Kley et al, 2004).

Introduction of Technique to Cat Owners

Owners are often worried when they learn that their cat is diabetic. At first they need to gain confidence that they will be able to manage the disease, get some basic understanding about diabetes, and learn how to inject insulin and they need to adapt their own lifestyle to the new needs of their cat. The immediate introduction

to home monitoring may overburden many owners and should therefore be delayed until the owner feels confident. We usually introduce the general concept of home monitoring by the time of discharge from the hospital after the diagnosis of diabetes has been made. Our written instructions on the various aspects of therapy also contain pictures on how capillary blood glucose can be taken. During the first reevaluation (approximately 1 week later), the importance of BGCs in the control of the disease is emphasized, and the owner is informed that the procedure of home monitoring can be started after the next reevaluation (2 to 3 weeks after diagnosis). Owners who are very keen to perform home monitoring and those who are familiar with capillary blood sampling (e.g., have another diabetic pet or are diabetics themselves) may start home monitoring earlier.

Teaching capillary blood sampling and the use of the PBGM device takes at least 30 minutes and should be performed by an experienced veterinarian or technician who has performed the procedure many times. The owner is taught how to use the lancing device and all relevant technical aspects of the PBGM device. Some PBGM devices come with very detailed information and an instructional DVD (e.g., the AlphaTRAK); the veterinarian can also refer the owner to one of the many websites demonstrating the technique. The owner should not leave the hospital before being able to generate a blood drop and to work the PBGM device correctly. Along with the PBGM device and test strips, we provide forms for recording the blood glucose values and show how the glucose concentration should be plotted. It is important that owners performing home monitoring have ready access to veterinary support if required.

Sampling Site, Lancing Device, and Portable Blood Glucose Monitoring Device

Capillary blood can be obtained from various sites. Initial studies showed that blood glucose concentrations obtained from the ear correlated very well with those from venous blood (Wess and Reusch, 2000). Recent comparison of blood glucose concentrations between different sampling sites (ear, metacarpal, and metatarsal pads) revealed only minor, insignificant differences (Zeugswetter et al, 2010). Sampling sites may therefore be rotated (i.e., if no blood can be obtained at one site, another one can be used). Our preferred site of sampling is the inner aspect of the pinna. The tip of the ear is held between thumb and index finger, and the entire surface of the outer pinna is held flat using the remaining fingers of the same hand. One may also place a cotton ball on the outside of the pinna. With the other hand, the lancing device is placed on a non-haired area of the pinna and triggered. We aim for capillary, not for venous blood, and therefore avoid lancing a vein. No bleeding is expected after capillary sampling, and therefore no pressure is needed after the puncturing procedure. Shaving, warming, or any other preparation is hardly ever needed (Wess and Reusch, 2000; Casella et al, 2002; Reusch, 2013). If the cat dislikes being touched at the ears, we use the metacarpal, metatarsal, or digital pads (Fig. 7-20). Others prefer to sample from the lateral ear margin on the outside of the pinna or use non–weight-bearing pads (wrist pads) instead of weight-bearing pads to avoid discomfort when walking or risk of infection with use of a litter box (Ford and Lynch, 2013). Several starter kits not only provide the PBGM device with test strips but also a lancing device with a certain number of lancets. Pharmacies offer devices of different gauge sizes and various depth settings. Which lancing device is used is a question of personal preference. The most important point is that the veterinarian or technician is familiar with the device and is able to convincingly demonstrate its use. Unfortunately, the lancing device Microlet Vaculance (Bayer Diagnostics) designed for use on alternative sites (i.e., not the fingertip) in humans is no longer available. The Microlet Vaculance developed a vacuum after lancing, which helped to suck out blood.

The first PBGM device was the Ames Reflectance Meter, patented in 1971 by the Ames company. It was almost 20 cm long and required a very large drop of blood. Since then, numerous models have been developed that are smaller, lighter, faster, and easier to handle. Modern PBGM devices have a memory capacity for the test results, and some allow data to be transferred to a personal computer. Various models require coding or calibration, which is the process of matching the PBGM device with the test strips. Usually, this is done by inserting a code strip or a code number into the meter each time a new batch of test strips is used. If done incorrectly, the readings may be inaccurate. Some models use a "no coding technology," meaning that the device is automatically calibrated and coded whenever a test strip is inserted. In human medicine, the quality control of PBGM devices is of continuous concern because the success of diabetes management depends largely on the reliability of the blood glucose measurements. The analytical quality of measurements can be compromised by operator and other procedural errors (e.g., dirty meters), hematocrit, altitude, humidity, ambient temperature, and lot-to-lot variability of test strips (Farmer, 2010; Nerhus et al, 2011; Baumstark et al, 2012). A number of accuracy standards have been proposed over the past decades. The most recent International Organization for Standardization (ISO) accuracy standards for PBGM devices used in humans (known as ISO 15197 criteria) state that 95% of the PBGM device measurements should fall within ± 15 mg/dL (0.84 mmol/L) of the reference method at blood glucose concentrations < 100 mg/dL (5.6 mmol/L) and within ± 15% of the reference method at blood glucose concentrations ≥ 100 mg/dL (Garg et al, 2013; International Organization for Standardization, 2013). However, those requirements are often not met. A recent study in humans showed that only 18 of 34 PBGM devices (52.9%) fulfilled those ISO standards (Freckmann et al, 2012).

A huge number of different PBGM devices are currently available, and most of them are made for use in humans. Unilke earlier times, most human PBGM devices are nowadays plasma-calibrated (i.e., they read the blood glucose concentrations from capillary [whole] blood as if they were plasma glucose concentrations). The reason behind this calibration is to enable better comparison between laboratory and PBGM device measurements. As the amount of glucose within erythrocytes in cats (and dogs) is lower than in humans, those PBGM devices may underestimate the "true" blood glucose concentration.

Several companies are now marketing devices for veterinary use, claiming that they give more accurate results in dogs and cats. We are currently using the PBGM meter, AlphaTRAK 2 (Abbott Animal Health), in the hospital and recommend its use to owners. This PBGM meter is also plasma-calibrated, taking into account the difference of glucose distribution in whole blood in dogs and cats (see www.alphatrakmeter.com for more information). So far, a small number of studies have compared the performance of the AlphaTRAK meter with those of several human PBGM devices and demonstrated that quality parameters were better for the AlphaTRAK (Cohen et al, 2009; Zini et al, 2009b). However, glucose readings from the AlphaTRAK may still differ considerably from the reference method, and differences increase as blood glucose concentrations increase. In contrast to many human PBGM devices, which usually give readings in dogs and cats that are lower than the reference method, the AlphaTRAK

FIGURE 7-20 Capillary blood sampling from the ear **(A** to **D)** and pad **(E)** of a diabetic cat.

may either under- or overestimate the "true" glucose concentrations. Therefore, unlike earlier times when the veterinarian could assume the "true" glucose level to be a bit higher than what is measured with the PBGM device, we now have to accept the concentration at face value. In most cases, the differences are small; in rare instances, however, hypoglycemia may be overlooked. In our most recent evaluation, using 78 feline samples, no difference between the AlphaTRAK reading and the reference method was found in 7 samples (9%). In 40 samples (51%), the AlphaTRAK overestimated the glucose concentration; the differences to the reference method ranged between 1.8 to 72 mg/dL, median 4.4 mg/dL (0.1 to 4.0 mmol/L, median 0.8 mmol/L). In 31 samples (40%), the AlphaTRAK underestimated the glucose concentration by (−1.8) to (−122) mg/dL, median (−12.6) mg/dL ([−0.1] to [−6.8] mmol/L, median [−0.7]). Table 7-8 shows the differences in the glucose categories < 100 mg/dL (5.6 mmol/L) and ≥ 100 mg/dL. Fortunately, precision of the AlphaTRAK is better at blood glucose concentrations < 100 mg/dL (5.6 mmol/L), where exact measurements are most important, and approximately 90% of values fall within ± 15 mg/dL (0.85 mmol/L) of the reference method. At blood glucose above 100 mg/dL (5.5 mmol/L) imprecision is higher but is less serious. It is usually of lesser importance to distinguish a blood glucose concentration of 200 mg/dL from 250 mg/dL (11 and 14 mmol/L) because treatment decision does not change or is minor.

The bottom line is that according to currently available data, the AlphaTRAK performs reasonably well in cats and dogs. Additional advantages are the very small sample volume (0.3 µL) and the wide measurement range of 20 to 750 mg/dL (1.1 to 42 mmol/L). The influence of factors (e.g., hematocrit, ambient

temperature, and others) known to have an impact on the precision of human PBGM devices have not yet been investigated for the AlphaTRAK with feline blood. Other "veterinary" PBGM devices are on the market, and many more will certainly come. It is very important that the veterinarian ensures that independent quality control studies have been performed before using them. A certain degree of deviation from the reference method, however, has to be accepted.

Problems and Long-Term Compliance

Many of our clients call for advice one or more times after the start of home monitoring. Some have specific questions regarding the procedure, and others just need reassurance that they are performing the procedure correctly. If support via telephone is insufficient, additionally, demonstration of the techniques should be provided. By watching an owner perform the procedure, the veterinarian or technician can identify and correct errors immediately. The most frequently encountered problem is failure to generate an adequate amount of blood. If repeated demonstration is unsuccessful, an alternative sampling site (e.g., switching form pinna to footpad) may be helpful. Handling the PBGM device is usually not a problem for owners, and most report that their cat tolerates the procedure quite well. As little restraint as possible should be used to avoid the cat becoming stressed. Usually, cats become accustomed to the procedure with time and increasing experience of the owner. Many owners try different strategies for easier restraint and report that their cats tolerate blood collection better when placed in a favorite spot, such as bed, window sill, and/or a confined area such as a sink.

Most owners are able to measure blood glucose without help, but a second person may be required initially. The skin puncture does not seem to be painful, and the puncture sites are barely visible, even after numerous blood collections. The exceptions are cats with very thin ears in which we have seen aural hematomas. In those cats, blood samples should be collected from the footpads. Long-term compliance with home monitoring is usually good, and many owners measure blood glucose on a regular basis for many years. The vast majority of owners highly appreciate their active participation in the management of the disease. Periodic reassessment of the entire procedure (capillary blood sampling, use of the PBGM device, and correct reading and interpretation of the measurements) in the hospital is highly recommended (Casella et al, 2002; 2005; Kley et al, 2004; Reusch et al, 2006a). However, home monitoring is an additional burden to owners that should not be underestimated. The veterinarian must carefully determine whether an owner is able (psychologically and time-wise) to cope with home monitoring and should keep in mind that owners may opt for euthanasia if they feel stressed. Owners should understand that home monitoring is an additional tool in the management of diabetes, which provides valuable information. It is not an absolute requirement. On the other hand, there are also "overmotivated" owners who absolutely want to have a perfectly regulated cat. Those owners tend to contact the hospital whenever a blood glucose value is outside the target range, even if the deviation is only slight. They need to understand that the blood glucose concentration in a diabetic individual is influenced by numerous factors and can vary from day to day. It is important that those owners learn to look at the general picture (well-being, stability of body weight, and most but not all glucose measurement within the target range) than on single glucose values. The exception is the finding of a very low glucose concentration, which requires an immediate reduction of the insulin dose. It has been assumed that cat owners who perform home monitoring would visit the hospital less frequently. However, our experience over the past 15 years does not support this assumption. Frequency of veterinary visits does not differ to a relevant degree among cats with and without home monitoring.

TABLE 7-8 **COMPARISON OF GLUCOSE CONCENTRATIONS MEASURED BY THE PORTABLE BLOOD GLUCOSE MONITORING DEVICE, ALPHATRAK, AND THE REFERENCE ANALYZER***

	Glucose Concentration Obtained with Reference Analyzer	
	< 100 mg/dL (5.6 mmol/L)	**≥ 100 mg/dL (5.6 mmol/L)**
AlphaTRAK		
Number of samples with no difference	4 (11%)	3 (7%)
Overestimation		
Number of samples	17 (49%)	23 (53%)
Range (median)	1.8 to 27 mg/dL (7.2) 0.1 to 1.5 mmol/L (0.4)	1.8 to 72 mg/dL (36) 0.1 to 4.0 mmol/L (2.0)
Underestimation		
Number of samples	14 (40%)	17 (40%)
Range (median)	(–1.8) to (–18) mg/dL (–5.4 mg/dL) (–0.1) to (–1.0) mmol/L (–0.3)	(–3.6) to (–122) mg/dL (–22 mg/dL) (–0.2) to (–6.8) mmol/L (–1.2 mmol/L)

*Data are given for glucose concentrations < 100 mg/dL (5.6 mmol/L) and ≥ 100 mg/dL. A total of 78 feline samples were analyzed; in 35 samples, blood glucose measured with the reference analyzer was < 100 mg/dL, and in 43 samples, blood glucose was ≥ 100 mg/dL.

Frequency of Monitoring

Our protocol for generation of a BGC at home is to have the owner measure the glucose concentration before the morning insulin injection and every 2 hours thereafter until the evening insulin injection is due. One of the several advantages of home monitoring is the fact that the veterinarian can ask for further blood glucose measurements in cats in which the glucose nadir is not reached during this time (e.g., generation of a 14- or 16-hour BGC) without interfering with working hours of the practice. More frequent measurement (hourly) may be suggested in cases with suspected hypoglycemia so that the lowest glucose concentration is not missed. In cats in which the diabetes is well controlled, the intervals may be prolonged to approximately every 3 hours—in particular during long-term management. Opinions on the question, "How often owners should check their cat's blood glucose?" differ. Some investigators have suggested that owners should perform measurements several times per day and adjust the insulin dose accordingly following a very tight dosing algorithm. Those algorithms are sometimes called *remission protocols,* and it has been claimed that following those protocols lead to higher remission rates (Roomp and Rand, 2009; 2012). There is little doubt that early and adequate treatment results in better diabetic control, fewer complications, and potentially to a higher remission rate compared with situations in which treatment is delayed and poorly done. However, those intensive protocols require owners who have the time to measure several times per day, and they bear a high risk of hypoglycemia,

even when performed under close supervision. The remission rate in our hospital using the protocol described here ranges between 40% to 50% over the years; this is only slightly lower than the rate of 51%, which was achieved with a "remission protocol" (Roomp and Rand, 2009), provided that cats with prior steroid treatment were excluded from the analysis. In cats that develop diabetes during steroid treatment, remission is often easily achieved after cessation of the drug and initiating insulin therapy, and remission rates may therefore appear to be high if many of those cats are included in a study. Our protocol foresees that owners generate a BGC once a week during the first months of therapy. After stabilization (and if no remission is achieved), the time intervals are prolonged to approximately every 3 to 4 weeks. We also ask owners to measure the fasting blood glucose (pre-insulin glucose) twice weekly and to perform a spot glucose check whenever they feel uncertain about the well-being of the cat. Although many of our owners work full-time, this protocol is feasible for most of them, because they generate the BGC during the weekend. There are cases in which we ask for additional BGCs (e.g., in an extremely unstable diabetic), but those are rare exceptions.

Interpretation of Blood Glucose Curves and Adjustment of Insulin Doses

Owners can certainly be taught how to interpret BGCs and to make adjustments in insulin dose. However, we prefer that decisions are made by the veterinarian and BGCs be sent to the hospital, especially during the first 3 months of therapy. This initial treatment period needs particular attention, because most cats require several dose adjustments. It is also during this time that either diabetic remission occurs or the presence of insulin resistance becomes apparent, requiring further work-up. During long-term management, owners may take more responsibility and make (slight) dose adjustments on their own.

BGCs are extremely helpful for the titration of the insulin dose, either upward or downward. Interpretation of BGCs generated at home follows the same rules as BGCs generated in the hospital. Our goal is to achieve blood glucose concentrations that are below the renal threshold by avoiding hypoglycemia. The highest glucose concentration, which is usually (but not always) the fasting/pre-insulin concentration, should not exceed 180 to 270 mg/dL (10 to 15 mmol/L); the lowest glucose concentration (glucose nadir) should ideally be between 80 and 140 mg/dL (4.5 to 7.8 mmol/L). Lower nadirs may be due to insulin overdose (including sudden improvement of insulin-resistant states), excessive overlap of insulin actions, or lack of food intake. They may also be found in cats in which diabetes is ready to go into remission or is already in remission. Finding a nadir below 70 mg/dL (3.9 mmol/L) should always lead to a reduction of the insulin dose. We tolerate the occasional occurrence of a nadir between 70 and 80 mg/dL (3.9 to 4.5 mmol/L) if the cat is doing well and is monitored closely. In general and in the long-run, however, nadirs should not be lower than 80 mg/dL (4.5 mmol/L). The dose reduction should be 0.5 to 1.0 U/cat b.i.d. if the cat is on a low to moderate dose of insulin (0.5 to 3/cat b.i.d.) or 25% to 50% if the cat is on a higher dose.

BGCs allow assessment of the insulin efficacy, the glucose nadir, and duration of the insulin effect. *Insulin efficacy* means the effectiveness of insulin to lower the blood glucose concentration, and it may be evaluated by determining the difference between the highest and lowest glucose concentration of a BGC. A small difference is acceptable when all blood glucose concentrations are well within the target range; however, it is not acceptable if this is not the case. Of note, the shape of BGCs differs considerably between cats and also within the same cat. Additionally, the type of insulin influences the shape of a BGC. With Lente-type insulins (Vetsulin/Caninsulin) and PZI oftentimes more or less bell-shaped BGCs with a pronounced peak are seen (i.e., the fasting glucose concentrations are substantially higher than the glucose nadirs). Long-acting insulin analogues (insulin glargine/Lantus, insulin detemir/Levemir) are so-called peakless insulins, which in theory should keep the blood glucose concentration at a fairly constant level. In fact, in some cats treated with insulin glargine, the BGC is flat. In others, however, a clear peak is seen. The shape of the BGC may change with time in the same cat. Initially, when glycemic control is still poor, blood glucose concentrations may just fluctuate in the high glycemic range; with improved glycemic control, a "true" curve is often seen, which again changes into a more or less flat line when good glycemic control or diabetic remission is achieved (Fig. 7-21).

The glucose nadir is an important parameter because it is the major determinant of dose adjustment. We titrate the insulin dose in steps of 0.5 U/cat b.i.d. until the glucose nadir is between 80 to 140 mg/dL (4.5 to 7.8 mmol/L). Dose requirements differ substantially between cats. Some are adequately controlled with an insulin dose as low as 0.5 U/cat b.i.d., and others need up to 1 U/kg b.i.d. or more. The majority of diabetic cats need between 0.5 and 3.0/cat b.i.d. Insulin requirements > 1.0 U/kg should raise suspicion for the presence of concurrent disease, and further work-up should be considered. However, some diabetic cats without concurrent disease may need quite high insulin doses (1.0 to 1.5 U/kg b.i.d.) during the initial phases of treatment, and oftentimes the dose can be cut back after some time. The reason is unclear; it is possible that those cats suffer from more serious glucose toxicity and/or insulin resistance, which may be

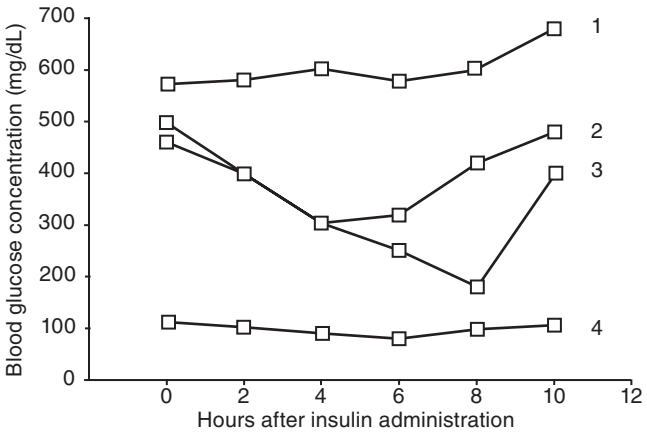

FIGURE 7-21 Change of blood glucose curve (BGC) shape in a diabetic cat (Devon Rex, castrated male, 9 years old, 4.5 kg) during treatment with insulin glargine (Lantus). *BGC 1:* 1 week after initiating treatment, insulin dose was 2.0 U/cat b.i.d.; *BGC 2:* 6 weeks after start of therapy, insulin dose was 4.5 U/cat b.i.d.; *BGC 3:* 10 weeks after start of therapy, insulin dose was 6.0 U/cat b.i.d.; *BGC 4:* 20 weeks after start of therapy, insulin dose was 0.5 U/cat s.i.d. Insulin administration was stopped at that time; diabetes is still in remission (2 years after cessation of insulin administration). The increase and decrease in insulin dose was done in steps of 0.5 U/cat b.i.d., and before each step, a BGC curve was generated. Here, only four BGCs are shown to demonstrate that the shape of the BGC may change during treatment. All BGCs were generated by the owner at home. Generally, although insulin glargine is considered a peakless insulin, some cats display a clear glucose nadir, whereas in others, the BGC resembles more a flat line. *0,* Time of insulin administration. To convert mg/dL into mmol/L, multiply blood glucose concentration by 0.056.

overcome with treatment. The duration of effect is defined as the time from the insulin injection through the glucose nadir until the blood glucose concentration exceeds 180 to 270 mg/dL (10 to 15 mmol/L), and it should be evaluated when the glucose nadir is within the target range and be ideally approximately 12 hours. If the duration is less than 8 to 10 hours, the cat usually reveals signs of diabetes; and if the duration is longer than 14 hours, the risk of hypoglycemia or the occurrence of the Somogyi effect increases (see Complications of Insulin Therapy).

Dose adjustments are generally done once a week after receiving the weekly BGC from the owner. The numbers of dose adjustments differ widely between diabetic cats. In some, one or two adjustments are sufficient to achieve the target glucose range, and in others, it takes several weeks. It is not uncommon that the need to increase the dose alternates with the need of dose reduction. In cats that continue to be severely hyperglycemic after the first 2 to 3 weeks, the process of dose increase is hastened slightly, and the intervals are shortened to approximately every 5 days. We do not change the dose more often than every 5 to 7 days (except in the case of hypoglycemia) because the insulin needs some time to equilibrate. Insulin glargine, which is currently our preferred insulin, is designed as intermediate/long-acting insulin. In humans, it is very often used in a treatment regimen, called *basal-bolus* or *multiple daily injection regimen.* Therewith, it is attempted to mimic the normal physiological secretion of insulin as close as possible by providing background basal insulin coverage (with insulin glargine) along with a bolus injection of short-acting insulin at each mealtime. In humans, it is recommended not to make changes more frequently than every 3 days, particularly for the basal insulin (Gough and Narendran, 2010). This means that intermediate/long-acting insulins are not designed for daily dose changes.

Basal-bolus regimens are usually not suitable for cats, and treatment is limited to the use of the basal insulin preparation. Due to the small size of our feline patients, the percentage of dose adjustment (even when done in small steps such as 0.5 U) is much bigger than what is done in humans. We therefore include a safety margin to avoid hypoglycemia by using a somewhat longer equilibration phase. When the blood glucose targets are reached in a particular cat, the question arises whether remission of the disease can be achieved or not. One may decide to leave the situation as it is and "wait and see." We sometimes consider to "push" it a bit further, and we discuss the pros and cons (chance of remission versus risk of hypoglycemia) with the owner. The decision mainly depends on the glucose nadir. If the nadir is in the lower range of what we regard ideal (e.g., 80 to 90 mg/dL, 4.5 to 5.0 mmol/L), we do not increase the dose. However, if the nadir is 95 to 140 mg/dL (5.3 to 7.8 mmol/L), we suggest increasing the dose by 0.5 U/cat b.i.d. The cat should be supervised closely during the following days, fasting blood glucose concentrations should be measured, and a BGC should be generated within a few days. If hypoglycemia occurs (blood glucose < 70 mg/dL, 3.9 mmol/L), the insulin dose is cut back again to the previous one.

The next challenge is to decide if remission has occurred. *Remission* is defined as the situation in which the clinical signs of diabetes have resolved, serum fructosamine and blood glucose concentration are in the normal range, and insulin therapy can be ceased. In cats in which all blood glucose measurements of a BGC range between 80 and 120 mg/dL (4.5 to 6.7 mmol/L) and serum fructosamine concentration is < 350 µmol/L, we start to reduce the insulin dose in steps of 0.5 U/cat b.i.d. every 5 to 7 days. The owner is advised to monitor the cat closely with regard to reappearance of clinical signs, and a BGC is performed prior to each reduction step. The insulin is reduced until a dose of 0.5 U/cat s.i.d. is reached; if the blood glucose is still normal, insulin administration is terminated.

Close clinical monitoring and regular glucose measurement (e.g., fasting blood glucose twice per week) is recommended to ensure that there is no relapse of the disease. Reduction is done in larger steps than 0.5 U/cat if hypoglycemia is seen. Besides the nadir, the fasting/pre-insulin blood glucose concentration is an important variable. Fasting blood glucose below the target range may be due to insulin overdose, improvement of an insulin-resistant state, overlap of insulin actions, or in case of diabetic remission. In those situations, we use the following as a rough guideline. If the fasting blood glucose is between 140 and 180 mg/dL (7.8 to 10 mmol/L), the cat should be fed, and in case the cat can be monitored throughout the day, the normal insulin dose should be administered; otherwise, the dose should be reduced by 0.5 U/cat. If the fasting blood glucose is between 80 and 140 mg/dL (4.5 to 7.8 mmol/L), the cat should be fed and the insulin dose reduced by 0.5 U/cat. If the fasting blood glucose is < 80 mg/dL (4.5 mmol/L), the cat should be fed and no insulin be given. Another glucose measurement should be performed after 1 to 2 hours. If the blood glucose is still < 80 mg/dL (4.5 mmol/L), no insulin should be given; if the blood glucose is > 80 mg/dL, a small dose (⅓ of the normal dose) should be administered. It should be understood that those cats need to be evaluated with regard to the cause of the low fasting blood glucose and to decide on the further insulin dose. It also needs to be understood that the protocol is a guideline and all decisions have to be made on an individual basis. Insulin sensitivity varies between cats and therefore some cats may require a more pronounced dose reduction. Reduction may also be more pronounced in cats receiving high doses of insulin.

Variability of Blood Glucose Curves

In humans, it is well known that blood glucose concentrations can vary markedly from day to day. These variations are associated with different levels of activity, emotional stress, and differences in meal size and composition. However, even when these factors are held constant, day-to-day variability may persist. Causes include variable rate of insulin absorption, variation in length of insulin activity, variation in insulin sensitivity, and remaining β-cell function. There is also substantial variability among BGCs of diabetic cats. When BGCs generated at home were compared with those generated in the hospital within the same week under the same conditions (i.e., same insulin dose and diet, same blood sampling conditions), treatment decisions would have been identical regardless of the BGC used in approximately 60% of cases, whereas in approximately 40% of cases, the decisions would have been different (Casella et al, 2005).

In a follow-up study, BGCs generated on 2 consecutive days at home and on 1 day in the hospital within the same week were compared. In some cats differences between the consecutive home BGCs were also relatively high and often not smaller than between home and clinic BGC. In cats with good glycemic control, variability between BGCs was less than in cats with moderate or poor glycemic control (Alt et al, 2007; see Fig. 7-19, *B*; Fig. 7-22). The bottom line is that single BGCs may not be totally reliable for treatment decisions, even when they are generated at home. However, one of the major advantages of home monitoring is that the veterinarian can ask the owner for more than one BGC before a treatment decision is made. This is of particular importance in cats that are difficult to regulate. Treatment decisions should never be made on the basis of glucose measurements alone, but they should always include the interpretation of the clinical situation.

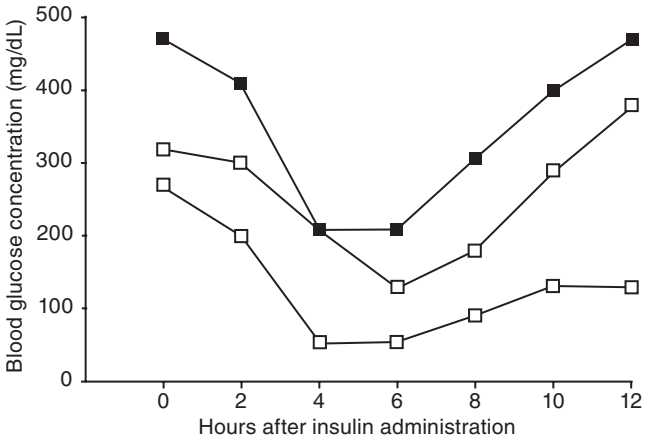

FIGURE 7-22 Variability of blood glucose curves (BGCs) generated at home and in the hospital in a cat (Siamese, castrated male, 14 years old, 6.1 kg) receiving 3.0 U Lente-type insulin (Vetsulin/Caninsulin) b.i.d. The two home-BGCs were generated on 2 consecutive days; the clinic-BGC was generated within the same week. The nadir in one of the home-BGCs was 54 mg/dL, which is too low. The nadir of the other home-BGC was 130 mg/dL, which is acceptable; however, several of the glucose concentrations measured throughout the day were too high. The nadir of the clinic-BGC was too high (210 mg/dL), as were all the other glucose concentrations. The cat was suffering from chronic pancreatitis, which may have been the cause of the variability. At the time the BGCs were generated, the cat had polyuria and polydipsia and reduced appetite, and serum fructosamine concentration was 560 μmol/L. The dose was not changed at this point in time, but had to be amended thereafter a few times (dose increase and decrease). With time, the clinical situation stabilized, blood glucose concentrations became more consistent, and serum fructosamine decreased to 427 μmol/L. In this case, a change to an insulin with a different activity profile (e.g. insulin glargine /Lantus) may have been a good alternative. These BGCs demonstrate that blood glucose concentrations should always be interpreted in conjunction with clinical signs. The advantage of home monitoring is that one or more additional BGCs can be generated before a treatment decision is made. *0,* Time of insulin administration. To convert mg/dL into mmol/L, multiply blood glucose concentration by 0.056.

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) systems were developed approximately two decades ago, and they have been introduced more recently into veterinary medicine (Davison et al, 2003; Wiedmeyer et al, 2003; Ristic, 2005). Those systems measure glucose concentrations in the subcutaneous interstitial fluid by using transcutaneous sensors. Interstitial fluid is easily accessible with transcutaneous sensors and has rapid equilibration with the blood, resulting in a good correlation of interstitial and blood glucose concentrations. Various different CGM systems are currently available, and as with the PBGM devices, many more are expected to become available in the future. The first systems (and some of the systems used until today) offered only retrospective analysis of the glucose concentrations after disconnecting the sensor and uploading the data, whereas newer generations measure and display the data immediately—real-time continuous glucose monitoring (RT-CGM). Immediate availability of results is a major advantage because it allows direct intervention. We evaluated various aspects of one of those real-time systems (Guardian REAL-Time system) and consider it to be a highly valuable additional monitoring tool. The system uses a small electrode, which is inserted in the subcutaneous tissue by means of a 22 G needle and fixed with tape after clipping and disinfecting a small area of skin. Thereafter, the sensor is connected to a transmitter that is also fixed to the patient with tape, and that sends data in a wireless fashion to a pager-sized monitor. Data are collected every 10 seconds, and a mean glucose value in the sensor is computed every 5 minutes and seen on the monitor (Figs. 7-23 and 7-24). Wireless transmission of data is only possible if the monitor is within 2 to 3 meters of the patient (e.g., is fixed to the cage). This is the major limiting factor of the device, because it limits the use for home monitoring. Theoretically, one could affix the monitor to the patient; however, the well-being of the cat would most likely be compromised. There are a few other limitations of the system. It requires a 2-hour period for initialization, and no data are provided during this time. The system then has to be calibrated; however, only glucose concentrations between 40 and 400 mg/dL (2.2 to 22.4 mmol/L) can be used for calibration. If the glucose is higher or lower, calibration has to be postponed until the blood glucose concentration is within the working range. Changes of blood glucose are followed by changes in interstitial blood glucose with a delay of approximately 11 minutes in cats (Moretti et al, 2010). Therefore, calibration should not be performed during times when blood glucose changes rapidly. Further calibration is needed 6 hours after initial calibration and then every 12 hours thereafter, which requires capillary or venous blood sampling. The sensor, which is quite expensive, has a limited sensor life; however, a complete restart of the system after the official lifespan of 72 hours allows another 72 hours of monitoring. Recently, a new sensor generation was marketed (Enlite Sensor, used with a different transmitter), which has a lifespan of 144 hours. The monitor displays glucose concentrations between 40 and 400 mg/dL (2.2. to 22.4 mmol/L); concentrations outside this range are correctly recorded but have to be downloaded to be seen.

Cats usually tolerate sensor placement and the bandage well, and usually no adverse skin reactions occur. Accuracy of measurements is an important issue, and none of the systems provides 100% accuracy. With the Guardian REAL-Time system, underestimation of blood glucose is more frequent than overestimation. Fig. 7-25 shows scatterplots of the differences between measurements with the CGM system and the PBGM device, AlphaTRAK, derived from 448 samples from diabetic (n = 39) and healthy cats (n = 5). Almost all measurements in the normo- and hyperglycemic range are clinically accurate (i.e., CGM system readings do not lead to a treatment error). In the hypoglycemic range, CGM system measurements deviate to a slightly larger extent from the reference measurement (Moretti et al, 2010). When simultaneous BGCs were generated with the Guardian REAL-Time system and the AlphaTRAK and analyzed in a blinded fashion by three internal medicine specialists, treatment decisions did not differ, supporting adequate accuracy for clinical use (Dietiker-Moretti et al, 2011). Readings differ depending on the site of the sensor placement. In cats, readings from the neck area have been shown to be more accurate than those from the lateral chest area or the knee fold. Additionally, initial calibration is more often successful when the neck is used. Technical problems include failure to successfully calibrate after the initialization period, discontinuation of recordings at some time during the long-term measurement (usually due to calibration errors) and loss of proper placement of the sensor underneath the skin (Hafner et al, 2013).

Currently, our main indication for the use of CGM system is blood glucose monitoring in diabetic cats that are hospitalized for several days (e.g., in case of DKA). The costs of the sensor and the 2-hour initialization period are major limitations for generation of BGCs on a routine basis. The great potential of those systems, however, is the possibility to continuously record blood glucose at home and thereby giving valuable information on the glycemic

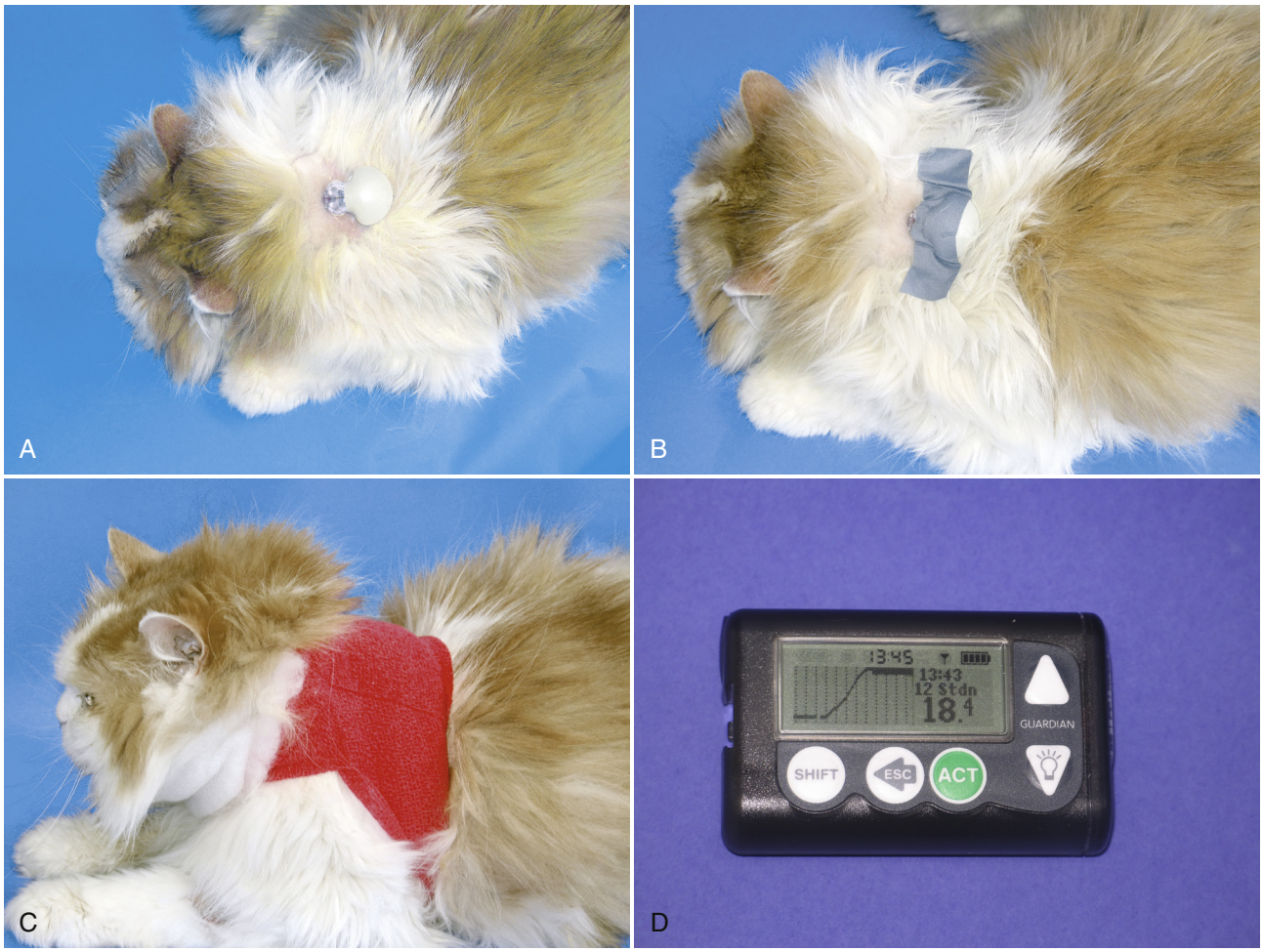

FIGURE 7-23 Use of the continuous glucose monitoring (CGM) system Guardian REAL-Time in a cat. **A,** Placement of the sensor in the subcutaneous neck area; the sensor is connected to the transmitter *(white).* **B** and **C,** Attachment with tape and bandage. **D,** Glucose concentrations are transmitted wirelessly to the monitor and displayed in real time. Here, the glucose given is 18.4 mmol/L (331 mg/dL).

situation during the night. With the current Guardian REAL-Time device, home monitoring is difficult, because the monitor has to be within 2 to 3 meters away from the patient. Various other wireless CGM systems also have a limited transmission range. The iPro system uses the same electrochemical sensor; however, the wireless transmitter used with the Guardian REAL-Time system is replaced by a recording device for data storage. Data are not recorded real-time but have to be downloaded. The device might be suitable for home monitoring, but it has not yet been evaluated in cats or dogs (Surman and Fleeman, 2013).

Insulin Therapy During Surgery

The approach to managing diabetic dogs and cats is similar and is discussed in Chapter 6 (see Insulin Therapy During Surgery).

COMPLICATIONS OF INSULIN THERAPY

Although the majority of diabetic cats can be adequately stabilized during the first 3 months of therapy, problems may occur any time during management. They usually fall within one of the following categories: stress hyperglycemia, hypoglycemia, technical errors, insulin underdose, insulin overdose with glucose counterregulation (Somogyi effect), short duration of insulin effect, prolonged duration of insulin effect, inadequate absorption of insulin, circulating insulin antibodies, fluctuating insulin requirements, and concurrent diseases causing insulin resistance.

Recurrence or persistence of clinical signs is a common problem requiring a logical and stepwise approach. The first step is to confirm that the cat indeed is poorly regulated (i.e., has clinical signs of diabetes such as polyuria, polydipsia, polyphagia, progressive weight loss, lethargy and decreased interaction with family members, lack of grooming behavior, and poor hair coat). High blood glucose levels may have been incorrectly interpreted to be the result of poor glycemic control when, in fact, they were stress induced. Fructosamine concentration is also not always a reliable parameter and is sometimes moderately or even markedly increased, although the cat is clinically well. Box 7-6 gives a stepwise approach to the work-up. Complications of insulin therapy are similar for diabetic dogs and cats; see Chapter 6 for a more comprehensive discussion.

Stress Hyperglycemia

Cats are prone to stress hyperglycemia, which develops as a result of an increase in catecholamines or may be due to increased gluconeogenesis stimulated by lactate release in struggling cats (Rand et al, 2002). Stress-induced hyperglycemia not only renders

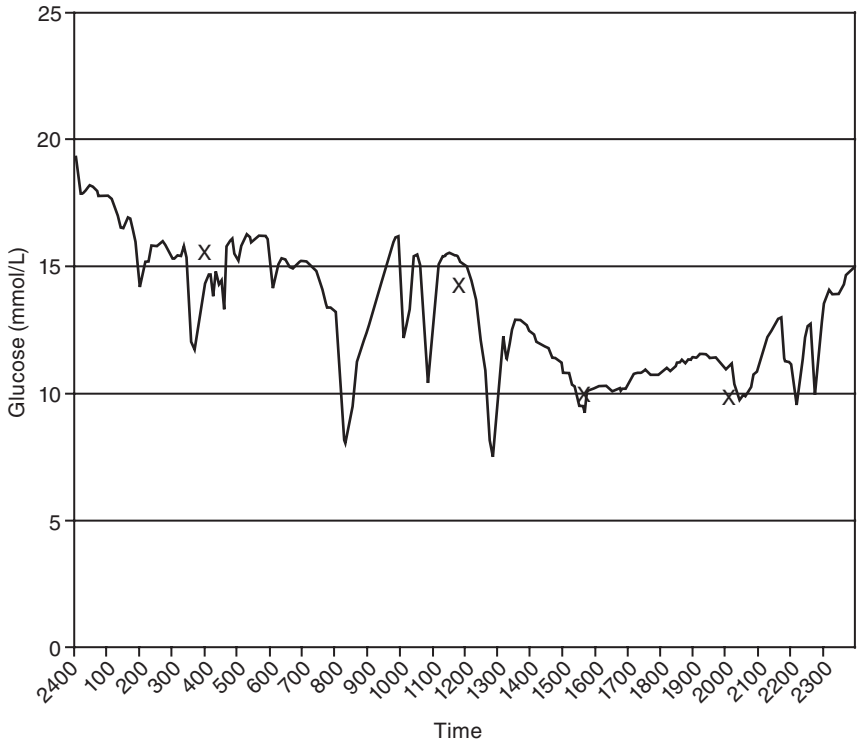

FIGURE 7-24 Blood glucose curve (BGC) over 24 hours generated by the continuous monitoring system Guardian REAL-time in a newly diagnosed diabetic cat after the start of insulin therapy. The curve is generated by the continuous glucose monitoring (CGM) system; X marks the glucose concentrations measured by the AlphaTRAK. To convert mmol/L to mg/dL, multiply by 18.

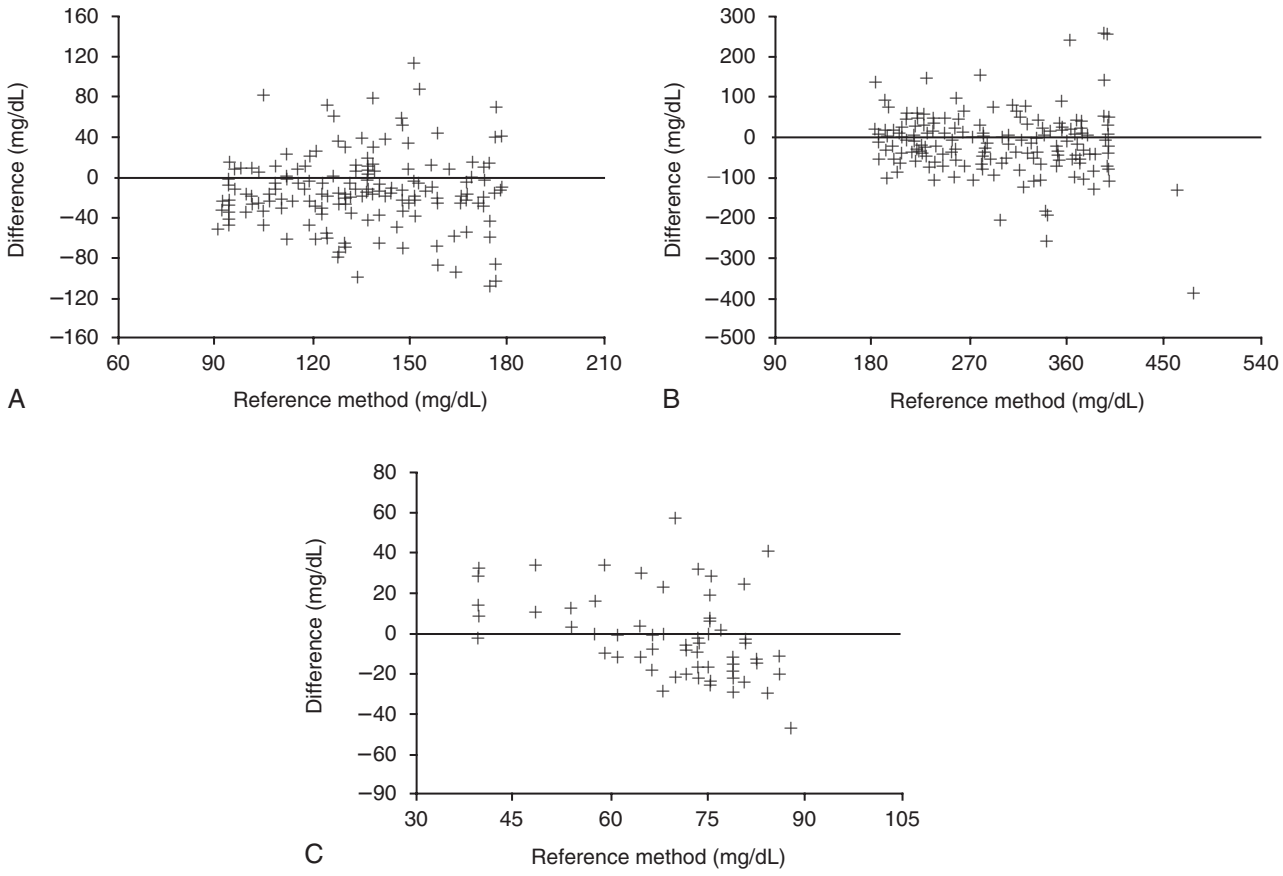

FIGURE 7-25 Scatterplots of the differences between blood glucose concentrations obtained by the use of the Guardian REAL-Time continuous glucose monitoring (CGM) system versus concentration obtained with the reference portable blood glucose monitoring (PBGM) meter AlphaTRAK at **(A)** normal, **(B)** high, and **(C)** low glucose concentrations in cats. To convert from mg/dL to mmol/L, multiply by 0.056. (From Moretti S, et al.: Evaluation of a novel real-time continuous glucose-monitoring system for use in cats, *J Vet Intern Med* 24:120, 2010 [with permission].)

BOX 7-6 Stepwise Work-Up in Diabetic Cats with Persistence or Recurrence of Clinical Signs

Step 1
- Confirm that the cat has clinical signs of diabetes.
- Determine whether work-up and previous treatment has been done according to the protocol (see Box 7-3).

Step 2
- Determine whether insulin used by owner is outdated, has been diluted, frozen, or heated.
- Determine whether appropriate syringes are being used (U 40/mL vs. U 100/mL).
- Assess owner's method of mixing, drawing up the correct dose, and injecting insulin.
- Review diet regimen.
  These points in problem-solving are often overlooked. However, technical errors are a frequent cause of difficulty in regulating a diabetic pet.

Step 3
- Increase insulin dose every 5 to 7 days until the cat receives a dose of approximately 1.0 U/kg twice daily (intermediate/long-acting insulin).

Step 4
- Generate blood glucose curves (BGCs) to determine whether there is the Somogyi effect or short duration of insulin effect. Blood glucose should be measured at home every 1 to 2 hours for at least 12 hours.

Step 5
- If no problem has been identified thus far, carry-out work-up for diseases causing insulin resistance. In principle, any other concurrent disease (e.g., inflammatory, infectious, or neoplastic) may cause insulin resistance. The most relevant problems are pancreatitis, pancreatic neoplasia, hyperadrenocorticism, hypersomatotropism (acromegaly), infections (e.g., of oral cavity or urinary tract), chronic renal failure, and obesity.
- As a last resort, poor absorption of insulin and circulating insulin antibodies should be considered. The relevance of the latter is controversial. Although insulin antibodies are produced (in particular when insulin of a different species is used), it is not yet clear to what extent they interfere with the action of the injected insulin. At this stage of the work-up, however, a switch to insulin of a different species is indicated.

diagnosis of diabetes difficult but also complicates the accurate evaluation of blood glucose concentrations measured during long-term management. Increases in blood glucose can range from mild to severe. Blood glucose levels may remain extremely elevated throughout the day despite insulin therapy or may start in an acceptable range and then steadily increase. Blood sampling can be extremely stressful for cats and is, therefore, a common cause of stress hyperglycemia. Failure to recognize the effect of stress on the blood glucose concentrations may lead to the erroneous assumption that the diabetic cat is poorly controlled. If insulin therapy is adjusted by increasing the dose, hypoglycemia or the Somogyi effect may result.

Stress hyperglycemia should be suspected, if there is a disparity between the assessment of glycemic control based on the owner's observations, body weight, results of physical examination, and the results of BGCs. Evaluation of serum fructosamine can provide additional valuable information, because the parameter is not influenced by a short-term increase of blood glucose. A fructosamine concentration within an acceptable range in a cat with no or little clinical signs is consistent with adequate glycemic control. If such a cat has highly elevated blood glucose concentrations, they are most likely stress-induced. In those cats, treatment decisions cannot be based on blood glucose levels. In our hospital, blood glucose is usually obtained from the pinna (as described earlier for home monitoring) by an experienced technician. The technique is usually well tolerated, and it is our impression that stress hyperglycemia is less of a problem with this technique. Stress hyperglycemia may also occur in the home environment if the owner has difficulty performing the procedure. However, in most cases, home monitoring is a good alternative to generation of BGCs in the hospital. See Establishing a Diagnosis of Diabetes Mellitus for more details on stress hyperglycemia.

Hypoglycemia

Hypoglycemia is the most serious complication of insulin therapy. It is the major factor that prevents achievement of near normoglycemia in diabetic patients with more tight glycemic control (i.e., increase of insulin dose), the risk of hypoglycemia increases. In humans, it is well established that the risk of hypoglycemia increases in proportion to the reduction of glycated hemoglobin. The positive effect of tight glycemic control is counterbalanced by fear and anxiety of hypoglycemia, reduction in quality-of-life, reduced productivity, and increased healthcare costs (Bilous and Donnelly, 2010; Fidler et al, 2011). Similarly, cat owners worry about hypoglycemia, and a survey identified fear of hypoglycemia as one of the main factors having a negative impact on the quality of the owner's life (Niessen et al, 2010). In a physiological state, hypoglycemia is prevented by inhibition of insulin secretion from the β-cells that occurs when the blood glucose declines in the postabsorptive phase. If the glucose level falls just below the normal range, secretion of counterregulatory hormones (in particular glucagon and epinephrine) is triggered. In humans, the threshold for the latter is a blood glucose concentration between 65 to 70 mg/dL (3.6 to 3.9 mmol/L). If these defenses fail to abort an episode of developing hypoglycemia, lower blood glucose levels lead to a more intense sympatho-adrenal response that causes neurogenic symptoms. Those symptoms cause awareness of hypoglycemia that prompts the behavioral defense mechanism of carbohydrate ingestion. In humans with diabetes, all of those defense mechanisms are typically compromised, a phenomenon known as *hypoglycemia unawareness* or *hypoglycemia-associated autonomic failure* (Cryer, 2010; 2013). An impaired counterregulatory response has also been documented in diabetic dogs (see Insulin Overdosing and Glucose Counterregulation [Somogyi Response]). If this phenomenon exists in diabetic cats, it has not yet been investigated. However, quite a substantial percentage of diabetic cats do not seem to sense hunger even if the blood glucose concentration decreases to quite low levels (e.g., < 50 mg/dL, 2.8 mmol/L); therefore, one should bear the possibility of failing defense mechanisms in mind. Hypoglycemia in diabetic cats is caused by an absolute or relative insulin excess. It results from insulin overdose, sudden increase in insulin sensitivity due to cure or improvement of concurrent disorders, diabetic remission that goes unnoticed, long duration of insulin action resulting in excessive overlap (mainly with PZI or insulin glargine, insulin detemir), or lack of food intake. Hypoglycemia may be a recurrent problem, most often seen in cats with concurrent disease in which phases of insulin sensitivity and insulin resistance alternate. Diabetic cats with chronic renal failure are notoriously difficult to regulate because insulin resistance due to uremic toxins coexists with reduced insulin clearance by the kidneys.

Hypoglycemia may be asymptomatic (biochemical) or symptomatic (clinical). There is no well-defined cutoff of blood glucose

below which hypoglycemia will become symptomatic. The lower the blood glucose and the more rapid the glucose level drops, the more likely clinical signs will be apparent. In cats, clinical hypoglycemia is more difficult to identify than in dogs. Hypoglycemic cats oftentimes just become quiet, withdraw from family life, and hide away. More obvious signs include restlessness, aggression, hunger, lethargy, weakness, salivation, muscle twitching, ataxia, seizures, and coma. Severe hypoglycemia may be fatal. Owners should be advised to treat symptomatic hypoglycemia depending on its severity either by offering food or administration of any of the various oral glucose gels (over-the-counter medication) or sugar water. Our owners do not inject glucagon in case of suspected hypoglycemia, although this option may be worth exploring (Niessen, 2012). If signs do not resolve immediately, the cat should be brought to the hospital and treatment performed as described in Chapter 9. Owners should also be advised to measure the blood glucose concentration in any of those situations. Documentation by the owner that hypoglycemia was present is very helpful for the veterinarian, because it may have resolved when the cat arrives in the hospital.

We consider blood glucose concentrations < 70 mg/dL (3.9 mmol/L) as too low, although clinical signs usually only occur when glucose levels are lower than 50 to 60 mg/dL (2.8 to 3.4 mmol/L). In cats showing symptomatic hypoglycemia, insulin administration should be discontinued until the blood glucose levels are > 180 mg/dL (10 mmol/L). Thereafter, insulin should be restarted with a dose reduced by approximately 50% per injection. In the case of asymptomatic hypoglycemia (e.g., hypoglycemia found by chance), the calculation of the dose reduction depends on the previous dose. If the cat was on a low to moderate insulin dose (0.5 to 3.0 U/cat b.i.d.), the dose should be reduced by 0.5 to 1.0 U/cat b.i.d.; if the cat was on a higher dose, reduction should be somewhat arbitrarily between 25% to 50%. Further monitoring and glucose measurements are mandatory to ensure that there are no further episodes of hypoglycemia and for the fine-tuning of the insulin dose. Some cats only need an insulin dose as low as 0.5 U/cat s.i.d.

Insulin Overdose and Glucose Counterregulation (Somogyi Effect)

The Somogyi effect is defined as rebound hyperglycemia due to hypersecretion of counter-regulatory hormones (mainly epinephrine, glucagon) during hypoglycemia, induced by a (slight) overdose of insulin. The phenomenon received its name after Michael Somogyi, a Hungarian biochemist. He postulated in 1959 that nocturnal hypoglycemia provokes rebound hyperglycemia and fasting hyperglycemia on the following morning in diabetic humans (Somogyi, 1959). In cats, the first description of the phenomenon was published in 1986 (McMillan and Feldman, 1986). Thereafter not much work on the Somogyi effect has been done, although it is frequently mentioned as an important cause of poor glycemic control. For the effect to occur, blood glucose levels must decrease to less than 65 mg/dL (3.6 mmol/L); however, it may also occur when the blood glucose concentration decreases rapidly regardless of the nadir (Fig. 7-26). Clinical signs of hyperglycemia are obvious, whereas signs of hypoglycemia often go unnoticed. Owners may report that days of good glycemic control are followed by several days of poor control, which should raise the suspicion of the Somogyi effect. Diagnosis requires the documentation of hypoglycemia or a very rapid drop in blood glucose concentration followed by hyperglycemia (blood glucose > 300 mg/dL, 17 mmol/L) within a 12-hour period. The hyperglycemic period can last 24 to 72 hours; the diagnosis may therefore be missed with a single BGC and accordingly, the incorrect assumption is made that the insulin dose is too low. Rebound hyperglycemia and the Somogyi effect should always be considered as a differential diagnosis when BGCs show persistently elevated blood glucose levels. To identify the problem, a series of BGCs is often needed, which may be best performed by home monitoring. If the Somogyi effect is documented or is assumed to be present, the insulin dose should be reduced—the degree of which is somewhat arbitrarily (0.5 to 1.0 U/cat b.i.d. in cats on a low to moderate dose, approximately 25% in cats on a higher dose of insulin). If no change is seen, a further slight dose reduction may be pursued. If clinical signs worsen, the approach was incorrect. Of note, classic glucose changes affiliated with this problem are not as apparent today as they were two to three decades ago, and this may reflect the changes in type of insulin used. We have seen a substantial number of cats in which the Somogyi effect was assumed to be the cause of the problem, but the cats were in fact suffering from a short duration of insulin effect. Lente-type insulins in particular may exert a pronounced peak with a quite fast decline in blood glucose concentration, but the effect is short lasting. In the latter situation, the shape of the BGC resembles a BGC showing the Somogyi effect. Close monitoring and generation of BGCs after the change of the insulin dose is therefore important. See the discussion on the Somogyi effect in Chapter 6 and the discussion on counterregulation in response to hypoglycemia in Chapter 9.

Technical Problems

Errors in injecting and handling insulin are frequent causes of poor glycemic control and include failure to mix the insulin correctly (if it is a suspension such as Vetsulin/Caninsulin or ProZinc), diluting, freezing or heating, use of outdated insulin, drawing up air instead of insulin, inappropriate insulin dose and timing, poor injection technique, and use of the wrong syringe size (U-40 mL vs. U-100/mL—a frequent error). Careful history taking, asking the owners to bring their own insulin and syringes, and watching the owner during the procedure will usually unravel the problem.

Insulin Underdose

Most cats are well regulated with insulin doses between 0.5 and 3.0 U b.i.d. (usually with ≤ 1 U/kg b.i.d.). Some diabetic cats may need insulin doses > 1.0 U/kg b.i.d.; however, this is oftentimes only temporarily during the initial phases of therapy and requirement decreases thereafter, which is most likely due to improvement of glucose toxicity. In general, insulin underdose should be considered if the insulin dose is considerably less than 1.0 U/kg b.i.d., and the dose should be increased. As mentioned earlier, we increase the insulin dose in steps of 0.5 U/cat b.i.d. every 5 to 7 days, and a BGC is generated before each step. The higher the insulin requirement, the more likely a concurrent disease is present, which causes insulin resistance. Further work-up should be pursued when the dose requirement is > 1.0 U/kg b.i.d.

Insulin underdose should always be considered if the cat receives the insulin only once daily. Duration of effect is usually never as long as 24 hours, independent of the type of insulin used, leaving the hepatic glucose production unopposed for a long time. In those cats, administration should be changed from s.i.d. to b.i.d., starting with a dose as recommended for the initial treatment (see Box 7-3).

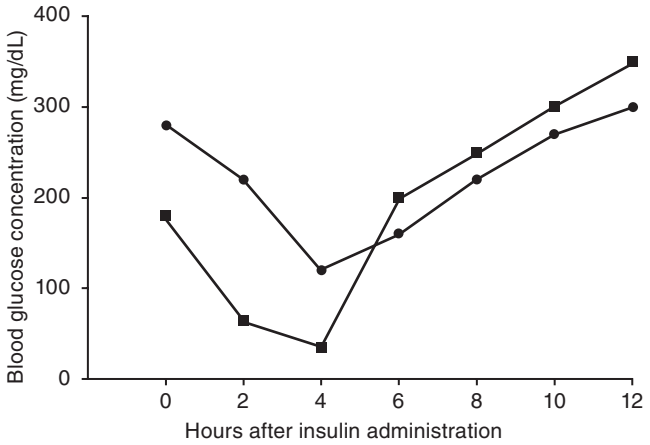

FIGURE 7-26 Blood glucose curve (BGC) 1 *(squares):* Suspected Somogyi effect in a diabetic cat (Domestic Short-Hair [DSH], spayed female, 12 years old, 5.9 kg) receiving 4.5 U/cat insulin glargine (Lantus) b.i.d. The blood glucose dropped to a nadir of 46 mg/dL within 4 hours of insulin administration, followed by an increase to 350 mg/dL within 8 hours. The effect did not reappear after reduction of the insulin dose to 3.5 U/cat b.i.d. BGC 2 *(dots):* Short duration of insulin effect in a diabetic cat (DSH, castrated male, 12 years old, 4.3 kg) receiving 1 U/cat Lente-type insulin (Vetsulin/Caninsulin) b.i.d. Short duration of effect is quite common in cats using this type of insulin. The change to another type of insulin with longer duration of action (e.g., insulin glargine) should be considered. Please note that BGCs displaying short duration of effect or the Somogyi effect may look quite similar. It is important to reevaluate the patient soon after amendment of treatment (e.g., dose reduction, change to another type of insulin) to make sure that the decision was correct. *0,* Time of insulin administration. To convert mg/dL into mmol/L, multiply blood glucose concentration by 0.056.

Short Duration of Insulin Effect

A short duration of insulin effect is a common cause of difficult to regulate diabetes in cats. It is almost always seen if the insulin is given once daily; however, it is also frequently encountered when given twice daily. NPH insulin preparations are notorious for their short duration of effect, and their use in cats is not recommended. However, short duration is also quite common in cats treated with Lente-type insulin (Vetsulin/Caninsulin). PZI insulin (ProZinc) and the long-acting insulin analogues (insulin glargine/Lantus, insulin detemir/Levemir) have longer duration of action, although twice daily administration is needed in the vast majority of cases (see also Long-Acting Insulin Analogues and Table 7-4). If duration of action is less than 8 to 10 hours, the cat usually has signs of diabetes. Diagnosis of duration of action requires generation of one or several BGCs, which is best done by home monitoring. Stress and reduced food intake in the hospital have a major impact on glucose values, rendering determination of duration of action nearly impossible. Duration of action should be assessed only if the blood glucose nadir is within the target range (80 to 140 mg/dL, 4.5 to 7.8 mmol/L), and should ideally be 10 to 12 hours. Diagnosis of short duration of action is confirmed by demonstrating blood glucose concentrations more than 180 to 270 mg/dL (10 to 15 mmol/L) within less than 10 hours of the insulin injection (see Fig. 7-26). Single glucose measurements (e.g., in the morning) are unsuitable and may lead to the erroneous assumption of insulin underdose. Fructosamine levels are usually moderately to severely increased. Treatment consists of changing to an insulin preparation with a longer duration of effect. For instance, if the cat is treated with Lente-type insulin (Vetsulin/Caninsulin), switching to PZI (ProZinc) or insulin glargine (Lantus) may solve the problem; if the cat is on insulin glargine and duration is too short, a change to PZI (ProZinc) or insulin detemir (Levemir) should be considered. Lente-type insulin is more potent than PZI and the long-acting insulin analogues, and therefore the change should be accompanied by a slight dose reduction (0.5 to 1.0 U/cat b.i.d.).

Prolonged Duration of Insulin Effect

Prolonged duration of insulin effect is a rather uncommon problem in diabetic cats. It is usually not seen with NPH or Lente-type insulin (Vetsulin/Caninsulin). It may, however, occur occasionally in cats treated with twice daily application of PZI, insulin glargine, or detemir. If duration of effect is longer than 12 hours, an overlap in insulin action results, which eventually leads to the Somogyi effect or to overt hypoglycemia. Indications for a prolonged duration of effect are a glucose nadir occurring 10 or more hours after insulin administration and constantly decreasing glucose concentrations beyond the time of the next insulin administration. An extended BGC (glucose measurements every 2 hours for 14 to 18 hours) will usually unravel the problem. In some cats, a slight dose reduction can counterbalance the prolonged effect. If this is unsuccessful or results in worsening of glycemic control, one should switch to an insulin preparation with shorter duration of effect. In exceptional cases, switching from twice daily to once daily administration is possible; however, duration of effect should be at least 20 hours.

Impaired Absorption of Insulin

Slow absorption was a frequent problem with Ultralente insulin, which is no longer available. The problem is not considered to be important with the insulin preparations used today.

However, insulin absorption is influenced by various factors, including hydration status, local blood flow in the area where the insulin is injected, obesity, size of the insulin dose, exercise, and environmental temperature. The unpredictability of insulin absorption was the stimulus for development of the new generation of insulins, the insulin analogues. Insulin analogues were designed for humans mainly to provide more consistent absorption kinetics. The currently available insulin analogues are still not perfect, and new analogues are under development. Repeated injection of insulin at the same location are known to result in local hypertrophy of adipose tissue in humans (called *lipohypertrophy*), which may result in slower and more erratic insulin absorption (Gough and Narendran, 2010). The same may be true for cats and therefore, the injection sites should be rotated. However, as blood flow differs, we advise that the body region should be held constant (e.g., lateral thoracic wall).

Binding of Insulin by Insulin Antibodies

Because the amino acid sequence of feline insulin differs to a varying extent from human, porcine, and bovine insulin (see Table 7-1), it is logical to assume that treatment will result in the production of anti-insulin antibodies. In principle, those antibodies are capable of binding circulating insulin and reducing its free concentration. If the antibody-insulin complex is subsequently removed by the reticuloendothelial system, the requirement for exogenous insulin may be extremely high. Alternatively, insulin may dissociate from the complex in an unpredictable manner, resulting in erratic concentrations of free insulin. Humans with diabetes produce anti-insulin antibodies even if they are treated

with human insulin. According to a comprehensive review, there is little proof that the development of insulin antibodies in humans affects glycemic control, insulin dose requirement, or the incidence of hypoglycemia, although the matter is somewhat controversial (Fineberg et al, 2007).

The relevance of anti-insulin antibodies in the management of diabetic cats has not been extensively investigated. Two studies identified antibodies in 14% and 37% of cats treated with recombinant human, beef, and beef/pork insulins. There was no correlation between glycemic control and the presence or absence of antibodies (Harb-Hauser et al, 1998; Hoenig et al, 2000a). Studies evaluating potential antibody production during therapy with the long-acting insulin analogues have not yet been performed in cats. The currently available data allow the assumption that problems in regulating diabetic cats are only rarely (if at all) due to anti-insulin antibodies. We consider the possibility that anti-insulin antibodies are the reason for the difficulty to regulate diabetes only as a last resort (i.e., we switch to an insulin preparation of a different species only after excluding the other causes of poor control).

Allergic Reaction to Insulin

Allergic reactions to insulin have not been documented in the cat. See Allergic Reaction to Insulin in Chapter 6.

Concurrent Disorders Causing Insulin Resistance and Drug-Induced Diabetes

Most diabetic cats can be regulated with insulin doses (intermediate-/long-acting insulin) between 0.5 and 3.0 U b.i.d. (usually with doses ≤ 1.0 U/kg b.i.d.). In cats with insulin requirements above this "threshold," concurrent disorders should be suspected provided that the problems discussed earlier (i.e., technical problems, short duration of effect) have been excluded. No insulin dose clearly defines insulin resistance. Insulin resistance should be suspected when glycemic control is poor despite insulin doses of more than 1.0 U/kg b.i.d., high doses (> 1.5 U/kg) are required to maintain blood glucose less than 270 mg/dL (15 mmol/L), and when glycemic control is erratic and insulin requirements constantly change. It is important to note that severity of insulin resistance can vary widely. Resistance can be mild and easily counterbalanced by some increase in insulin dose; however, it can also be severe requiring very high insulin doses or can fluctuate with time. See Concurrent Disorders Causing Insulin Resistance in Chapter 6 for more details on mechanism of insulin resistance and on insulin dose adjustment. Any inflammatory, infectious, neoplastic, and endocrine disorder can cause insulin resistance, as well as obesity and administration of insulin-antagonistic drugs. In cats, insulin resistance is most commonly caused by severe obesity, chronic renal failure, chronic pancreatitis, stomatitis/oral infections, hyperadrenocorticism, and hypersomatotropism (acromegaly). The latter two diseases are the ones with the potential of the most severe insulin resistance. Some of the causes will be obvious after obtaining a detailed history (e.g., administration of progestagens or glucocorticoids) and performing a thorough physical examination (obesity, stomatitis/oral infection). If history and physical examination are fruitless, CBC, serum biochemical panel, lipase/fPLI serum T_4 concentration, measurement of insulin-like growth factor-1 (IGF-1), urinalysis and urine culture, and abdominal ultrasonography should be the next steps. Additional tests (e.g., biopsy of a mass or organ abnormality, low-dose dexamethasone test) may be required. Insulin resistance may, at least in part, be reversible. Therefore, the administration of progestagens or glucocorticoids should be ceased. In case of obesity, a weight-reduction program should be instituted, and all treatable diseases should be managed as well as possible. Close monitoring is mandatory, because the insulin requirement may decrease substantially. With some disorders, such as chronic renal failure and chronic pancreatitis, insulin resistance persists or continues to fluctuate, and glycemic control usually remains challenging. In those cases, teaching the owner about the latter will help to avoid frustration. The glucose targets should be set less tight, and the insulin dose chosen with the aim of avoiding hypoglycemia, very severe hyperglycemia, and DKA. Home monitoring of blood glucose is helpful to amend the insulin dose during acute flares or worsening of the disease.

Obesity

See Obesity under Dietary Management, and also see Obesity, Gender, and Other Risk Factors.

Chronic Pancreatitis

Acute flares of chronic pancreatitis may need in-hospital treatment including IV fluid therapy (with potassium supplementation), plasma transfusions, pain management, nutritional support (tube feeding), antiemetic, and antibiotic therapy. Long-term treatment of chronic pancreatitis is difficult, and a complete cure is often not possible. Suggested measures include the use of appetite stimulators (mirtazapine, cyproheptadine), cobalamine supplementation (if deficient), and supplementation with antioxidants (S-adenosylmethionine [SAMe], vitamin C, vitamin E, and/or selenium). In humans with acute pancreatitis, the use of glucocorticoids is currently under investigation. There are anecdotal reports on clinical improvement when used in cats with chronic or chronic relapsing pancreatitis (Armstrong and Williams, 2012). However, there are currently no criteria that would help the clinician to decide which cat would potentially benefit from a short-term steroid administration and in which cases it would cause harm.

Chronic Kidney Disease

See Concurrent Disorders Causing Insulin Resistance in Chapter 6.

Hyperthyroidism

See Serum Thyroxine Concentration.

Exogenous Glucocorticoids and Progestins

Glucocorticoids were named for their hyperglycemic effects, and they have the potential to exert strong diabetogenic properties. They may induce hyperglycemia in previously normoglycemic patients as well as worsen glycemic control in patients already known to have diabetes mellitus. Glucocorticoids induce or worsen diabetes mellitus by increasing insulin resistance in peripheral tissues (muscle, fat) and by increasing hepatic glucose production. Additionally, they may inhibit insulin release from the β-cells (Delaunay et al, 1997; Gittoes et al, 2010; Lowe et al, 2009). In humans, overt diabetes or impaired glucose tolerance is seen in 14% to 28% of individuals receiving long-term glucocorticoids. Humans who are not able to increase their insulin secretion to counterbalance the effects of the glucocorticoid (i.e., have an intrinsically low insulin secretion capacity) are particularly susceptible (Wajngot et al, 1992; Gittoes et al, 2010). In cats, the prevalence of overt diabetes during glucocorticoid therapy has not yet been systematically evaluated. Steroid diabetes can occur after oral or parenteral as well as after topical administration of any of the currently available glucocorticoids. Glucocorticoid sensitivity

varies between individual cats and therefore dose, duration, and frequency of application that will ultimately lead to hyperglycemia, cannot be predicted. Experimental studies have shown that abnormalities may already become apparent after short-term therapy. Administration of 2 mg/kg prednisolone s.i.d. for 8 days resulted in reduced glucose tolerance after an IV glucose load in all six cats, and three of the six developed hyperglycemia (Middleton and Watson, 1985). It has been suggested that dexamethasone has greater diabetogenic effects than equipotent doses of prednisolone (Lowe et al, 2008; 2009). Steroid diabetes often goes into remission, provided that the glucocorticoid application is ceased immediately and insulin treatment is initiated. Careful monitoring of blood glucose levels is important. After the effect of the glucocorticoid on insulin sensitivity wears off, the insulin requirement decreases, resulting in the need to also decrease the insulin dose. Remission may fail to appear if treatment is inadequate or if the cat has substantial islet pathology. If glucocorticoid therapy cannot be terminated and no alternative drug can be used, the insulin dose has to be adjusted on the severity of the insulin resistance. In those cases, glycemic control oftentimes remains difficult.

Progestins are known to exert glucocorticoid activity, and they have similar effects to glucocorticoids on insulin sensitivity. Treatment with progestins (e.g., megestrol acetate) may therefore also result in glucose intolerance or overt diabetes (Peterson, 1987; Middleton and Watson, 1985; Middeleton et al, 1987). Other glucocorticoid-like side effects including skin atrophy, alopecia, and skin lacerations may be seen as well. Similar to glucocorticoids, it is not possible to predict which cat will develop diabetes, and therefore, regular reevaluations are mandatory. Remission of diabetes may occur after discontinuation of progestin administration and the initiation of insulin therapy.

Hypersomatotropism (Acromegaly)

Hypersomatotropism is a disease that is almost always associated with diabetes mellitus. It has the potential to cause very severe insulin resistance and requirements of insulin doses more than 2 U/kg b.i.d. are no exception. Insulin resistance, however, can also be quite mild, in particular in the initial phases of the disease. Hypersomatotropism in cats is caused by a GH-producing tumor (usually an adenoma) in the pars distalis of the pituitary gland. GH has catabolic and anabolic effects; the latter are in part mediated by IGF-1. The catabolic effects are mainly due to insulin antagonism and are the reason for the diabetes mellitus. The anabolic effects include proliferation of bone, cartilage, soft tissue, and organs resulting in a large body size, broad head and large paws, weight gain, prognathia inferior, respiratory difficulties because of thickening of pharyngeal tissues, degenerative arthropathy, and organomegaly with potential organ dysfunction. Growth of the tumor may lead to signs of a central nervous system (CNS) disease. Of note, clinical signs may also be very subtle or even absent, and the disease may therefore be overlooked. Acromegaly has long been considered a rare disorder. However, it was recently suggested that acromegaly occurs more frequently than previously thought and is most likely underdiagnosed (Niessen et al, 2007). Because the availability of a validated GH assay for cats is a problem, diagnosis is usually based on the finding of a high IGF-1 concentration. A few important points should be kept in mind. First, circulating IGF-1 is bound to proteins, which must be removed before measurement. Not all methods are equally effective, and intra-assay inference of binding proteins may lead to falsely high IGF-1 levels (Tschuor et al, 2012). Therefore, only assays validated for the cat should be used. Second, IGF-1 concentrations are often low in newly diagnosed diabetic cats and increase markedly after initiating insulin therapy. Low IGF-1 levels have also been seen initially in untreated diabetic cats with acromegaly (Reusch et al, 2006b). In our hospital, IGF-1 is measured 6 to 8 weeks after initiating insulin therapy. Because IGF-1 measurements are not 100% reliable, the final diagnosis requires documentation of a pituitary mass by CT or magnetic resonance imaging (MRI) scan. See Chapter 2 for more details.

Hyperadrenocorticism

Hyperadrenocorticism is considered to be a rare disease and is associated with diabetes mellitus in approximately 80% of cats. Pituitary-dependent disease is present in 75% to 80%, and 20% to 25% suffer from a cortisol-secreting adrenocortical tumor. In rare circumstances, adrenocortical tumors secrete steroid hormones other than cortisol. Progesterone-producing tumors result in clinical signs that are identical to those caused by hypercortisolism, and they may also be associated with diabetes mellitus (Boord and Griffin, 1999; Rossmeisl et al, 2000; Quante et al, 2009). In addition to polyuria/polydipsia (pu/pd) and weight loss, which are usually due to concurrent diabetes mellitus, typical clinical signs are abdominal enlargement, an unkempt seborrheic hair coat, thinning of the hair coat, failure of hair to regrow or alopecia, and muscle weakness. Severe cases may have thin fragile skin that tears easily. Cats with large pituitary masses may have CNS disturbances. However, clinical signs may also be mild, and hyperadrenocorticism is often not suspected until it becomes evident that the diabetes is difficult to regulate. The dexamethasone suppression test is the preferred screening test. Whether poorly-regulated diabetics have hyperactivity of the hypothalamus-pituitary-adrenal gland axis that leads to false positive test results is controversial. We recently investigated the dexamethasone test in a group of diabetic cats 6 weeks after initiating insulin therapy. In 20 of 22 cats, the cortisol concentration was completely suppressed at 4 and 8 hours after the application of 0.1 mg/kg dexamethasone IV. The results did not differ between cats with good glycemic control and those with moderate to poor control. In two cats, the test was abnormal and hyperadrenocorticism was confirmed by histopathology (Kley et al, 2007). Based on our results, the dexamethasone test appears to be a suitable part of the diagnostic work-up in diabetic cats suspected of having hyperadrenocorticism. In our hospital, we perform testing for hyperadrenocorticism in cats in which glycemic control remains difficult after several weeks of therapy and other problems have been excluded. Usually, the test is carried out 6 to 8 weeks after initiating insulin therapy. Further details on feline hyperadrenocorticism can be found in Chapter 11.

Fluctuating Insulin Requirements (Glycemic Instability)

One of the most frustrating problems encountered with insulin therapy is the inability to maintain glycemic control. For instance, previously well-regulated cats on a stable dose of insulin suddenly develop clinical signs of diabetes and severe hyperglycemia; an increase in insulin dose may solve the problem for a short time, after which further dose amendments (either increase or decrease) are required. Other cats suffer from recurrent flares of DKA, despite being closely monitored, and have to be brought to the hospital as an emergency frequently. Another subset of diabetic cats suffers from frequent episodes of hypoglycemia that alternate with phases of adequate control or hyperglycemia. In humans, the same problems occur and the term *brittle diabetes* is used for individuals with glycemic instability sufficient to disrupt the patient's lifestyle. Causes of "brittleness" are numerous and include failure to follow treatment regimen correctly,

inappropriate lifestyle and dietary management, recurrent infections, gastrointestinal diseases, chronic pancreatitis, concurrent endocrinopathies or administration of diabetogenic drugs, impaired counterregulatory hormone secretion, delayed gastric emptying due to autonomic neuropathy, genetic defects in or beyond the insulin receptor, and psychiatric and psychological problems. In some patients, no obvious cause is found, which is then called *idiopathic brittle diabetes* (Voulgari et al, 2012). Most of those causes are also known to cause difficulties regulating diabetes in cats and have already been discussed. Most commonly, glycemic instability in cats is due to acute flares of chronic pancreatitis or the development of another concurrent disease (infections, neoplasia, chronic renal disease), severity of which can range from mild (and may be overlooked) to severe. Any disease may increase insulin resistance, and if insulin dose is not adequately increased, signs of diabetes reoccur and DKA may develop. After improvement or resolution of the concurrent disease, insulin resistance decreases, which may result in hypoglycemia if the insulin dose is not amended. Cats with glycemic instability need a thorough work-up as discussed earlier (see also Box 7-6). If a cause cannot be identified, close monitoring is mandatory, and regular home monitoring of blood glucose is of great help to decide on insulin dose amendments.

CHRONIC COMPLICATIONS OF DIABETES MELLITUS

Systemic Hypertension

There is currently no convincing evidence that diabetes in cats is associated with clinically relevant hypertension. Of eight cats with recently-diagnosed diabetes, two had increased systolic blood pressure of 170 and 180 mm Hg. However, values of 170 and 180 mm Hg were also found in two of 20 healthy control cats (Sander et al, 1998). Similar findings were described in 14 cats with a median diabetes duration of 18 months. None of the cats had systolic blood pressures more than 180 mm Hg, and blood pressures of healthy controls and diabetic cats did not differ. None of the cats had proteinuria or retinopathy (Senello et al, 2003). These findings are in agreement with two other studies, in which the duration of diabetes was not specified; however, none of the 13 cats examined had hypertension (Bodey and Sansom, 1998; Norris et al, 1999). In a more recent study, the prevalence of hypertension was not different in diabetic cats compared to control cats (Al-Ghazlat et al, 2011). Nevertheless, there may be exceptional cases. In one study, two diabetic cats with hypertensive retinopathy were described; one had evidence of renal dysfunction, which may have been the cause of hypertension, but the other cat had no other concurrent disease (Maggio et al, 2000). Further studies using larger cohorts of diabetic cats are needed to evaluate questions, such as the definitive prevalence of hypertension and the risk of kidney-damage when blood pressure is in the upper end of normal (Reusch et al, 2010).

Diabetic Cataracts

For a long time it was believed, that diabetic cataract does not develop in cats. A recent study demonstrated, however, that cataract formation is in fact a frequent event in feline diabetics. Forty-eight of 50 cats (96%) with diabetes had some degree of lens opacification. In 22 of them (46%), the findings were limited to linear posterior cortical opacification, which is similar to what is seen in normal, elderly cats. Twenty-six cats (54%), however, had more pronounced cortical cataracts or posterior subcapsular plaques. Severity of diabetic cataracts differs substantially between dogs and cats, as none of the cats was blind (Williams and Heath, 2006). Therefore, different from diabetic dogs, cataract formation in diabetic cats is usually of limited clinical relevance. More severe cataract with potential blindness may develop in diabetic kittens (Thoresen et al, 2002). The enzyme aldose reductase and the sorbitol pathway seem to play an important role in formation of diabetic cataract. (See Chronic Complications of Diabetes Mellitus in Chapter 6.) It has been shown that aldose reductase activity is significantly lower in lenses of older cats than in younger cats and dogs, which may prevent serious cataract formation (Richter et al, 2002).

Diabetic Nephropathy

In humans, diabetic nephropathy is a well-known and extremely serious complication of diabetes. It is a chronic disease developing over many years and is characterized by gradually increasing urine protein excretion and blood pressure, which is later followed by a decline in glomerular filtration rate and azotemia. Urine protein excretion itself gradually increases from microalbuminuria to overt proteinuria, and the development of overt nephropathy takes many years (Marshall and Flyvberg, 2010). Histopathological lesions affect predominantly the glomeruli, but there may also be severe interstitial and vascular involvement. Findings include thickening of the glomerular basement membrane, mesangial expansion, nodular sclerosis (Kimmelstiel-Wilson lesions), tubular basement membrane thickening, mononuclear cell infiltrates in the interstitium, interstitial fibrosis and atrophy, and arteriolar hyalinosis (Tervaert et al, 2010). Chronic renal disease is common in the elderly, non-diabetic cat population, and its cause is usually unknown. Diabetes is also relatively common in elderly cats. So far, it is unclear if diabetes in cats leads to kidney damage and chronic renal failure or if the coexistence of the two diseases is just coincidence. In recent studies, the prevalence of chronic renal disease in diabetic cats ranged between 17% and 63% (Roomp and Rand, 2009; 2012; Callegari et al, 2013). In a group of newly diagnosed diabetic cats, 13.3% developed chronic renal failure during a 6-month follow-up study (Hafner et al, 2013).

Proteinuria is assumed to be a marker for progression of chronic renal disease and high urine protein-to-creatinine (UPC) ratios have been shown to predict the development of azotemia in non-diabetic cats (Jepson et al, 2009; Chakrabarti et al, 2012). In diabetic cats, the prevalence of proteinuria was recently shown to be significantly higher than in healthy and sick, non-diabetic controls (75%, 18%, 34%). None of the cats were azotemic by the time of urinalysis, and no follow-up information with regard to potential progression to chronic renal failure was given (Al-Ghazlat et al, 2011). One small study reported histopathological findings in six diabetic cats, which consisted of mesangial proliferation in two cats, and glomerular sclerosis and interstitial inflammation in one cat each (Nakayama et al, 1990). We recently compared histopathological findings in 32 diabetic cats to those of 20 matched control cats. Glomerular lesions were observed in 17 (53%) of diabetic cats and 12 (60%) of the controls and consisted mainly of increased mesangial matrix, glomerular basement membrane thickening, and thickening of the Bowman capsule. Tubulointerstitial lesions were demonstrated in 26 (81%) of the diabetic and 16 (80%) of the controls and included interstitial fibrosis, inflammation, atrophy, and necrosis; vascular abnormalities were found in 3 (9.4%) of the diabetic and 2 (10%) of

the controls. Statistical analysis revealed no difference between the groups. Of note, tubule-interstitial necrosis tended to be more frequent in diabetic cats than in controls (50% and 25%); however, the difference did not reach significance. Based on those results, it is very likely that cats do not develop diabetes-induced nephropathy. The short life expectancy of diabetic cats and the low prevalence of hypertension may be main reasons for the difference from human diabetics (Zini et al, 2014). If proteinuria is found in a diabetic cat, the next step is to exclude urinary tract infection and hypertension as possible causes. Thereafter, one should aim for good glycemic control and perform regular reevaluations. If severity of proteinuria increases, treatment with angiotensin converting enzyme (ACE) inhibitors may be considered, although data on their benefit in cats are scarce. Treatment of chronic renal failure in diabetic cats should follow the same guidelines as in non-diabetic cats.

Diabetic Neuropathy

Diabetic neuropathy is one of the most common chronic complications of diabetes in cats. The vast majority (90%) of diabetic cats reveal nerve abnormalities if peripheral nerves are examined by electron microscopy (Dahme et al, 1989). Overt neurological signs, however, are seen in only approximately 10% of cats. Clinical signs range from very mild to severe and include hind limb weakness, difficulty or inability to jump, a base-narrow gait, ataxia, muscle atrophy most noticeable in the distal pelvic limbs, and a plantigrade posture when standing and walking, postural reaction deficits and decreased tendon reflexes, and irritability when the feet are touched or manipulated. Clinical signs may progress to include the front legs with a palmigrade stance and gait (Mizisin et al, 2002; see Box 7-2). By means of electrophysiological testing, decreased motor and sensory nerve conduction velocities can be demonstrated with more severe decrease in diabetic cats with severe clinical neuropathy. Thoracic limbs tend to be less severely affected than the pelvic limbs, and sensory nerve conduction is less severely affected than motor nerve conduction. Electromyographic abnormalities are usually absent or if identified, are consistent with denervation (Mizisin et al, 2002; 2007).

Histological evaluations of nerve biopsies display concurrent injury to both Schwann cells and axons of myelinated fibers, which is remarkably similar to lesions in human diabetic neuropathy. Schwann cell injury is mainly characterized by splitting and ballooning of the myelin sheath and subsequent demyelination. Additionally, disproportionally thin myelin sheath can be found, being indicative of episodes of remyelination following demyelination and suggests ongoing metabolic dysfunction. Axonal injury consists of axoplasmic dystrophic accumulation of membranous debris and glycogen as well as degenerative fibre loss. Similar axonal injuries can be found in unmyelinated fibers (Dahme et al, 1989; Mizisin et al, 1998; 2002; 2007). Recently, it was shown that nerve fibre injury in diabetic cats is also associated with endoneurial microvascular abnormalities, some of which parallel those in human diabetic neuropathy (Estrella et al, 2008).

The pathogenesis of diabetic neuropathy is only incompletely understood and most likely multifactorial. Most data are derived from studies with diabetic rodent models. Potential mechanisms include increased flux through the polyol pathway, accumulation of advanced glycation end products on nerve and/or vessel proteins, disturbances in n-6 essential fatty acids and prostaglandin metabolism resulting in abnormal nerve membranes and microvasculature, depletion of nerve growth factors, and inflammatory as well as immunological processes (Ziegler, 2010). Data in cats are scarce. One study demonstrated an increase in nerve glucose and nerve fructose suggesting increased polyol pathway activity (Mizisin et al, 2002). The first step in the polyol-pathway is the reduction of glucose to sorbitol by the enzyme aldose reductase; thereafter, the enzyme sorbitol dehydrogenase oxidizes sorbitol to fructose. It is currently assumed, that those enzymatic steps consume NADPH, which is an important cofactor to regenerate reduced glutathione. The latter in turn is an important scavenger of reactive oxygen species (ROS); thus reduction in NADPH could induce or worsen oxidative stress (Giacco and Brownlee, 2010). Interestingly, in humans with type 1 diabetes, intensive treatment and enhanced glycemic control significantly reduces the risk for developing diabetic neuropathy, whereas in type 2 diabetics, glucose control has only small effects on the prevention of neuropathy (Callaghan et al, 2012). These data suggest that other factors (e.g., obesity, hyperlipidemia, and hypertension) are important contributors to the risk of diabetic neuropathy. Once diabetic neuropathy is established, intensive treatment and even diabetic remission does not result in significant improvement in humans. Various drugs have been studied (including aldose reductase inhibitors), but no major breakthrough has been achieved. Treatment is therefore mainly limited to pain relief; reduction in neuropathic pain has been seen with the use of antioxidants, such as alpha lipoic acid, acetyl-L carnitine, and benfotiamine (Smith and Singleton, 2012; Singleton and Smith, 2012). There is currently no recommended treatment for neuropathy in diabetic cats. In some cats, good glycemic control results in improvement of neurological signs, in others, however, no effect is seen. Complete reversal of diabetic neuropathy is a rare event. Lipoic acid may also show some effects in diabetic cats, however, it is associated with an increased risk of hepatotoxicity and should not be used until further studies on dosing regimens are available (Hill et al, 2004).

PROGNOSIS

The prognosis depends in part on owner commitment to treat the diabetes, presence of concurrent diseases (e.g., pancreatitis, chronic renal disease, and acromegaly), and the ease of glycemic control including the avoidance of complications such as DKA. In a recent study, survival time and prognostic factors were evaluated in 114 cats with newly diagnosed diabetes (Callegari et al, 2013). Mortality rate during the first 10 days was 16.7%, and the main causes of death were severe concurrent diseases. The rate compares quite well with mortality rates of 11% seen during the first weeks in previous studies (Kraus et al, 1997; Goossens et al, 1998). Median survival time was 516 days (range 1 to 3468 days), 70%, 64%, and 46% lived longer than 3, 6, and 24 months, respectively. Survival time was shorter for cats with concurrent diseases; increased serum creatinine concentrations at diagnosis was significantly associated with a poor outcome. Cats that achieved diabetic remission had longer survival times than cats that were persistently diabetic (Callegari et al, 2013). From those data, one may conclude that prognosis of diabetes in cats is moderate at best. However, two points have to be considered. First, cats are usually already quite old when diabetes is diagnosed, and second, the studies mentioned earlier were performed in referral centers, and data therefore are most likely associated with a negative selection bias. In cats without severe concurrent diseases, good quality of life can often be achieved for several years.

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