

## Perspective

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## What's in a Name? Classification of Diabetes Mellitus in Veterinary Medicine and Why It Matters

C. Gilor, S.J.M. Niessen, E. Furrow, and S.P. DiBartola

Diabetes Mellitus (DM) is a syndrome caused by various etiologies. The clinical manifestations of DM are not indicative of the cause of the disease, but might be indicative of the stage and severity of the disease process. Accurately diagnosing and classifying diabetic dogs and cats by the underlying disease process is essential for current and future studies on early detection, prevention, and treatment of underlying disease. Here, we review the current etiology-based classification of DM and definitions of DM types in human medicine and discuss key points on the pathogenesis of each DM type and prediabetes. We then review current evidence for application of this etiology-based classification scheme in dogs and cats. In dogs, we emphasize the lack of consistent evidence for autoimmune DM (Type 1) and the possible importance of other DM types such as DM associated with exocrine pancreatic disease. While most dogs are first examined because of DM in an insulin-dependent state, early and accurate diagnosis of the underlying disease process could change the long-term outcome and allow some degree of insulin independence. In cats, we review the appropriateness of using the umbrella term of Type 2 DM and differentiating it from DM secondary to other endocrine disease like hypersomatotropism. This differentiation could have crucial implications on treatment and prognosis. We also discuss the challenges in defining and diagnosing prediabetes in cats.

**Key words:** Canine; Feline; Insulin; Pancreatitis; Prediabetes.

### What Is Diabetes Mellitus?

Diabetes Mellitus (DM) is not a single disease, but a syndrome characterized by hyperglycemia that results from defects in insulin secretion or insulin sensitivity in target tissues or both.<sup>1</sup> Several pathogenic processes can lead to development of DM, from autoimmune destruction of pancreatic  $\beta$ -cells with consequent absolute insulin deficiency to abnormalities that result in resistance to insulin action such as hypersomatotropism. Regardless of cause, deficiency in insulin or its action on target tissues leads to a myriad of abnormalities in carbohydrate, fat, and protein metabolism. Abnormalities in insulin secretion and action frequently coexist in the same individual, and often it is impossible to determine which abnormality is the primary cause of the hyperglycemia. Also, deficits in insulin secretion are not necessarily merely a consequence of insulin resistance in individuals with type 2 DM (T2DM). The presence and magnitude of hyperglycemia can change over

*From the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH (Gilor, DiBartola); Department of Clinical Science and Services, Royal Veterinary College, University of London, North Mymms, Hertfordshire UK (Niessen); Department of Veterinary Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, MN (Furrow).*

*Corresponding author: Dr C. Gilor, Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, 601 Vernon Tharp Street, Columbus, OH 43210; e-mail: gilor.1@osu.edu.*

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### Abbreviations:

ADA	American Diabetes Association
BG	blood glucose concentration
DLA	dog leukocyte antigen
DM	diabetes mellitus
FPG	fasting plasma glucose concentration
FPIR	first phase insulin response
fPLI	feline pancreatic lipase activity
GH	growth hormone
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c concentration
HLA	human leukocyte antigen
HNF	hepatocyte nuclear factor
IDDM	insulin-dependent diabetes mellitus
IFG	impaired fasting glucose
IGF-1	insulin-like growth factor-1 concentrations
IGT	impaired glucose tolerance
IVGTT	IV glucose tolerance test
MODY	mature-onset diabetes of the young
NIDDM	noninsulin-independent diabetes mellitus
OGTT	oral glucose tolerance test
PGHDM	progesterone-controlled GH overproduction DM
PP	pancreatic polypeptide
RI	reference interval
T1DM	type 1 DM
T2DM	type 2 DM

time, depending on the extent of the underlying disease process and associated comorbidities. A disease process could cause prediabetes (see definition later) without progressing to overt diabetes.<sup>1</sup> Thus, the clinical and clinicopathologic manifestations of DM are not indicative of the cause or causes of the disease, but might be indicative of the stage and severity of the disease process. In this respect, it seems prudent to consider the diagnosis of DM as analogous to a diagnosis of other end-stage organ failures like chronic renal failure or hepatic cirrhosis.

Accurately diagnosing and classifying diabetic dogs and cats by the underlying disease process is essential for current and future studies on treatment methods, early detection, treatment of underlying disease, and prevention. Neonatal DM in people provides an example of how the specific underlying etiology can impact treatment recommendations. Until recently, diabetic neonates were considered insulin-dependent and prone to ketosis. This clinical presentation led to categorizing them as having insulin-dependent diabetes mellitus (IDDM) or type 1 DM (T1DM). Children therefore were relegated to life-long exogenous insulin treatment. This changed when it was discovered that most neonatal DM patients carry mutations in genes encoding the  $\beta$ -cell  $K_{ATP}$  channel. Once diagnosed correctly, such patients can be managed with oral sulfonylurea drugs, which allow them to become insulin-independent, achieve superior glycemic control and experience improved quality of life.<sup>2</sup> Similarly, advances in the study of autoimmune DM (T1DM) now allow targeted therapy that slows progression of the disease and decreases insulin requirements if used early enough in the disease process.<sup>3,4</sup> On the horizon are diagnostic tests for earlier detection of T1DM as well as studies on the prevention of the disease before establishment of an autoimmune state.<sup>5</sup>

### Classification of Diabetes Mellitus: Historical Perspective

The clinical manifestations of DM were first described by the Greeks over 2,000 years ago. From the first demonstration of lesions in the islets of Langerhans by Opie (1901) to the first successful use of insulin therapy by Banting and Best (1922), and throughout most of the 20th century, DM was classified based on clinical manifestations as juvenile or adult onset. In 1979, the National Diabetes Data Group proposed a new 3 category classification based on clinical manifestations and insulin requirement necessary to prevent ketosis: Insulin-dependent DM (IDDM, or juvenile DM, prone to ketosis), noninsulin-independent (NIDDM, or mature-onset DM, including Mature-Onset Diabetes of the Young [MODY], not prone to ketosis), and others (DM secondary to pancreatitis, endocrinopathies, drugs, and other causes).<sup>6</sup> Impaired glucose tolerance (IGT) and Gestational DM were classified separately.<sup>6</sup>

With increased understanding of the pathophysiology of DM toward the end of the 20th century, the terminology of IDDM and NIDDM was slowly replaced by type 1 and type 2 DM. Initially, the clinical categorization overlapped completely with etiologic type (ie, IDDM was termed type 1 and NIDDM was termed type 2), but at the turn of the century, the consensus was to adopt an etiology-based classification and the terms IDDM and NIDDM were abandoned.<sup>7</sup>

An up-to-date classification of DM from the American Diabetes Association (ADA) is presented in Table 1.<sup>1</sup> In this etiology-based classification, regardless of the underlying disease process, DM begins with a subclinical phase in which euglycemia is maintained,

**Table 1.** Etiologic classification of diabetes mellitus based on the American Diabetes Association (rare etiologies were not included).<sup>1</sup>

Type	Abbreviated description of etiology
1	$\beta$ -cell destruction, usually leading to absolute insulin deficiency <ol style="list-style-type: none"> <li>a. Immune-mediated</li> <li>b. Idiopathic</li> </ol>
2	<i>Unknown etiology.</i> A combination of insulin secretory defect with insulin resistance (Relative insulin deficiency)
Others	<ol style="list-style-type: none"> <li>a. Monogenic defects of <math>\beta</math>-cell function:               <ul style="list-style-type: none"> <li>MODY 1-8: Mutations in <i>HNF-1</i>, <i>HNF-4</i>, <i>glucokinase</i>, and others</li> <li>Transient neonatal: Mutations in <i>ZAC/HYAMI</i></li> <li>Permanent neonatal: Mutations in <i>KCNJ11</i></li> </ul> </li> <li>b. Genetic defects in insulin action</li> <li>c. Diseases of the exocrine pancreas</li> <li>d. Endocrinopathies:               <ul style="list-style-type: none"> <li>Insulin resistance (hypersomatotropism, hypercortisolism, others)</li> <li>Decreased insulin secretion (somatostatinoma, others)</li> </ul> </li> <li>e. Drug or chemical induced (diazoxide, cyclosporine, tacrolimus, others)</li> <li>f. Infections</li> <li>g. Uncommon forms of immune-mediated diabetes mellitus (Anti-insulin receptor antibodies, Stiff-man syndrome, others)</li> <li>h. Other genetic syndromes associated with diabetes (Down, PW, others)</li> </ol>
Gestational	A state of increased insulin resistance superimposed on an already existing state of $\beta$ -cell dysfunction or loss
Prediabetes	<i>Intermediate stages</i> in the disease processes of any of the above types

but abnormalities in  $\beta$ -cell function or mass already are present. As the disease progresses, glucose intolerance (impaired fasting glucose [IFG], IGT, or both) can be detected and a diagnosis of prediabetes made. With further progression, glucose intolerance worsens until the criteria for a diagnosis of DM are met. The line between prediabetes and DM however is arbitrary, and glucose intolerance progresses as a continuum (see later: Prediabetes and diabetes risk). In the diabetic state, insulin therapy might or might not be required, and the requirement could be permanent, transient, or recurring. Whether or not insulin is required, therefore does not define the disease category and is not unique to a disease category.<sup>1</sup> For example, although most patients with T1DM are insulin-dependent, they often experience a transient phase of insulin independence. Similarly, most people with T2DM initially are insulin-independent, but ultimately proceed to requiring insulin. Most often, this insulin-requiring state is temporary in T2DM, but also could become permanent.

Key features of each type of DM and prediabetes based on the current ADA classification are presented in the next section and subsequently are discussed in the context of DM in dogs and cats.<sup>1</sup>

## Classification of Diabetes Mellitus in Human Medicine

Overt diabetes mellitus (as opposed to prediabetes) is defined as a fasting plasma glucose concentration (FPG)  $\geq 126$  mg/dL (7 mmol/L), a plasma glucose concentration  $\geq 200$  mg/dL (11.1 mmol/L) 2 h after oral glucose administration, or a hemoglobin A<sub>1c</sub> concentration (HbA<sub>1c</sub>)  $> 6.5\%$ .<sup>8</sup>

### *Type 1 Diabetes Mellitus: Beta Cell Destruction Typically Leading to Absolute Insulin Deficiency*

**Immune-Mediated Diabetes Mellitus.** This form of T1DM results from cell-mediated autoimmune destruction of the pancreatic  $\beta$ -cells. In people, markers of the immune destruction of  $\beta$ -cells include several islet cell autoantibodies (GAD65, IA-2, and ZnT8) and autoantibodies to insulin.<sup>9</sup> Ninety-eight percent of T1DM people are autoantibody positive.<sup>8</sup> Two or more of these autoantibodies are present in 85–90% of T1DM patients when fasting hyperglycemia is detected, and antibodies can be detected years before onset of clinical disease. The antibody profile is highly predictive of the rate of progression to overt DM.<sup>9</sup>

The disease has strong human leukocyte antigen (HLA) class II associations, with linkage to the *DQA1*, *DQB1*, and *DRB1* genes.<sup>10</sup> These *HLA-DR/DQ* alleles can be predisposing or protective, and account for most of the heritability observed in T1DM. Several genes involved in T-cell function, including *PTPN22*, *CTLA4*, and *IL2RA*, also impart risk of T1DM. The insulin gene, *INS*, is another major non-HLA susceptibility gene, and polymorphisms in *INS* are strongly associated with the presence of insulin autoantibodies at diagnosis.<sup>9</sup> T1DM also is associated with other autoimmune disorders, including endocrine diseases as well as myasthenia gravis, autoimmune hepatitis, and inflammatory bowel disease.<sup>1,8</sup>

The rate of  $\beta$ -cell destruction is variable in immune-mediated DM. Whereas rapid progression is seen in juveniles, the disease progresses slowly in adults, and residual  $\beta$ -cell function might be retained for years.<sup>1</sup> In contrast to the original definition of juvenile-onset DM, 50% of T1DM patients are adults ( $>20$  years of age).<sup>8,11</sup> The disease in adults can be easily confused with T2DM because  $\beta$ -cell function often is sufficient to prevent ketoacidosis. Eventually, these patients become dependent on insulin. The “honeymoon phase” (a transient and partial remission phase in which a previously insulin-dependent patient does not require insulin therapy) often lasts 3–6 months, but might continue for 2 years, and occurs in up to 60% of T1DM patients.<sup>12</sup>

**Idiopathic DM.** In this subtype 1 DM, there is evidence of  $\beta$ -cell destruction, but without evidence of autoimmunity. An absolute requirement for insulin therapy can be intermittent. A minority of T1DM patients falls into this category and most are of African or Asian ancestry. This form of DM is strongly inherited, lacks features of  $\beta$ -cell autoimmunity, and is not

HLA-associated. For these reasons, recently the ADA excluded this subtype from the T1DM class.<sup>8</sup>

### *Type 2 DM: Unknown Etiology. Pathogenesis: A Combination of Insulin Secretory Defect with Insulin Resistance*

Type 2 DM previously was encompassed by NIDDM or adult-onset DM. Its pathogenesis is characterized by a combination of impaired insulin secretion with insulin resistance (relative insulin deficiency). Initially (and often throughout life), these patients do not require insulin treatment to survive. Although the specific etiologies are not known, autoimmune destruction of  $\beta$ -cells does not occur, and patients do not have any of the other causes of DM listed below for other specific types (ie, T2DM is a diagnosis of proactive exclusion).

Several mechanisms have been suggested as partial explanations for the abnormalities in glycemic control observed in T2DM patients, including amylin misfolding and amyloid deposition, decreased  $\beta$ -cell mass,  $\beta$ -cell dysfunction, decreased sensitivity to glucose, and  $\alpha$ -cell dysfunction.<sup>7</sup> Not all of these abnormalities are consistently present nor do they have the same degree of severity in all T2DM patients. Furthermore, the inciting lesions have not been clearly distinguished from the pathologic sequelae. Nevertheless, the various combinations of abnormalities likely represent different disease etiologies underlying T2DM. T2DM is a diagnosis of exclusion; whenever a primary disease process is identified, this type of DM is automatically excluded from the umbrella term T2DM and reclassified (see for example MODY below).

Most patients with T2DM are obese either by traditional weight criteria or by increased body fat in the abdominal region (ie, visceral obesity).<sup>7</sup> Although obesity causes insulin resistance, in itself it is not the cause of T2DM. In nondiabetic people, obesity results in a compensatory response in  $\beta$ -cells and a subsequent increased capacity to secrete insulin. Obese people remain euglycemic, but with increased insulin concentrations. In human autopsy studies, obese nondiabetic subjects have a 50% increase in relative  $\beta$ -cell volume.<sup>13</sup> In T2DM, this compensatory response to insulin resistance fails because of an intrinsic abnormality in  $\beta$ -cells. Although T2DM patients could have plasma insulin concentrations that are normal or increased, they are not as high as expected based on their blood glucose concentrations (BG). Insulin sensitivity might improve with weight reduction, pharmacologic interventions, or both, but it rarely normalizes.

Other risk factors for developing T2DM include aging and lack of physical activity. T2DM occurs more frequently in women with prior Gestational DM and in people with hypertension or dyslipidemia, and its frequency differs among ethnic groups. T2DM has a stronger genetic predisposition than autoimmune T1DM, with heritability up to 80%.<sup>14</sup> However, specific genetic risk factors for T2DM are diverse and complex, and remain to be fully elucidated.



### Other Specific Types of DM

**Monogenic Defects of the  $\beta$ -Cells.** Several forms of DM are associated with monogenic defects in  $\beta$ -function. This potentially is the most important category for clinicians to recognize.<sup>15</sup> Identification of the causative mutation can affect treatment recommendations and allow insulin therapy to be replaced by alternative pharmacologic interventions.<sup>15</sup>

**Neonatal DM: Transient or Permanent.** In contrast to past assumptions, DM diagnosed in the first 6 months of life in people is not caused by an autoimmune process and these patients are not necessarily insulin-dependent. Transient neonatal DM is characterized by hyperglycemia that begins in the neonatal period and resolves by 18 months of age.<sup>16</sup> The most common cause is a genetic defect at the *6q24* locus, resulting in overexpression of the genes that regulate insulin secretion,  $\beta$ -cell proliferation, and peripheral insulin sensitivity.<sup>16,17</sup> Permanent neonatal DM is a distinct condition commonly caused by mutation in the genes (*KCNJ11* and *ABCC8*) that encode subunits of the  $\beta$ -cell  $K_{ATP}$  channel. Children with this type of DM are not insulin-dependent; sulfonylurea therapy results in superior glycemic control.<sup>2</sup>

**Maturity Onset Diabetes of the Young.** Maturity onset diabetes of the young is characterized by impaired insulin secretion with minimal or no defects in insulin action. Affected patients typically are nonobese young adults (<25 years old). Genes implicated in MODY are crucial in  $\beta$ -cell development, function and regulation, as well as glucose sensing, and include the insulin gene.<sup>18</sup> The causative mutations are inherited in an autosomal dominant pattern. Up to 80% of MODY cases are caused by mutations in the glucokinase and hepatocyte nuclear factor (*HNF1A* and *HNF4A*) genes.<sup>19</sup> Treatment varies based on the underlying genetic defect. For example, patients with glucokinase gene mutations might have only mild hyperglycemia and not require any treatment, whereas those with *HNF1A* or *HNF4A* mutations require sulfonylurea therapy and might progress to insulin dependence.<sup>19</sup> Before genetic characterization, these patients were classified as having T2DM because the diagnosis was made in autoantibody-negative NIDDM adults.

**Genetic Defects in Insulin Action.** Genetic disorders of insulin receptors or postreceptor defects are uncommon in people and have not been reported in animals.<sup>1,7</sup>

**Diseases of the Exocrine Pancreas.** Any process that diffusely injures the pancreas has the potential to cause DM. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic neoplasia. Damage to the pancreas must be extensive before diabetes ensues (This type of DM is discussed more extensively below in the section relating to DM in dogs).

**Endocrinopathies.** Endocrinopathies that lead to severe insulin resistance can cause DM (eg, hypersomatotropism, hypercortisolism, glucagonoma, and pheochromocytoma). In these diseases, DM typically develops in people with preexisting defects in insulin secretion,

but hyperglycemia might resolve when hormone concentrations normalize.<sup>15</sup> Rarely, DM is caused by non- $\beta$ -cell endocrinopathies that decrease insulin secretion (eg, aldosteronoma-induced hypokalemia and somatostatinomas). Hyperglycemia generally resolves after removal of the tumor.

### Gestational DM

For many years, Gestational DM was defined as glucose intolerance that is first recognized during pregnancy, without distinguishing between cases in which glucose intolerance antedated pregnancy and those in which it developed concomitantly with pregnancy. Recently, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended that high-risk women found to have DM at their initial prenatal visit receive a diagnosis of overt, not Gestational, DM.<sup>20</sup> Thus, the diagnosis of Gestational DM is reserved for women that have had no evidence of DM in early pregnancy but developed it later during pregnancy. Most Gestational DM cases resolve after delivery.<sup>1</sup>

Gestational DM is an important diagnosis because it is associated with increased risk of complications during late pregnancy, abnormalities in the newborn, and future T2DM in the mother. Gestational DM represents a state of increased insulin resistance superimposed on an already existing state of  $\beta$ -cell dysfunction or loss.<sup>15</sup> Late in pregnancy, the human placenta secretes human placental lactogen and tumor necrosis factor- $\alpha$ , which lead to insulin resistance. As a result, insulin secretion increases to maintain euglycemia. Any cause of  $\beta$ -cell dysfunction or loss (ie, independent of etiology) could prevent this compensatory increase in secretion and lead to glucose intolerance or overt DM.<sup>15</sup>

### Prediabetes and Diabetes Risk

Prediabetes is defined as a condition in which hyperglycemia is present but does not meet criteria for DM. One or both of the following abnormalities are used to characterize a patient with prediabetes:

**Impaired fasting glucose (IFG):** FPG concentrations of 100–125 mg/dL (5.6–6.9 mmol/L).

**Impaired glucose tolerance (IGT):** 2-hour plasma glucose concentrations during an oral glucose tolerance test (OGTT) of 140–199 mg/dL (7.8–11.0 mmol/L).

Prediabetes (IFG, IGT, or both) indicates a high risk for the future development of DM as well as cardiovascular disease. IFG and IGT can be observed as intermediate stages in the disease processes of any DM type (type 1, 2, or others) and are associated with obesity (especially visceral obesity), dyslipidemia, and hypertension. Structured lifestyle intervention, increasing physical activity and 5–10% loss of body weight, as well as specific pharmacologic interventions can prevent or delay development of DM in people with prediabetes.

Prospective studies have identified a strong, continuous association between measures of glycemia and development of DM. Thus, the aforementioned cutoffs for IFG and IGT are arbitrary and intended merely to facilitate classification and enable comparison of studies. Studies on HbA<sub>1c</sub> (glycated hemoglobin) further demonstrate the continuum of risk for DM.<sup>21</sup> People with HbA<sub>1c</sub> above the laboratory reference interval (6.0–6.5%), but below the diagnostic cut-off for DM (>6.5%) have a high incidence of DM with 10-fold the risk of the general population. However, individuals at the high end of the RI (ie, 5.5–6.0%) also have a 3–8 fold increased risk. Therefore, preventive interventions are recommended at HbA<sub>1c</sub> > 5.5% even though results might fall within the normal range.

### Classification of Diabetes Mellitus in Veterinary Medicine

The classification system of IDDM and NIDDM was adopted by veterinary medicine in the 20th century and, as in human medicine, subsequently was replaced by the terminology types 1 and 2. At that time, however, the rationale for this change in terminology was not uniformly adopted. Many veterinarians continued to use the terminology Types 1 and 2 as equivalent to IDDM and NIDDM, regardless of the underlying etiopathogenesis. This is explained partially by the still modest (but gradually increasing) level of understanding of the underlying disease processes in the field of veterinary diabetology. Several questions arise when trying to apply the current DM classification based on etiopathogenesis to companion animals. What are the actual causes of DM in dogs and cats, and do the causes actually affect treatment? If so, how? Would a better understanding of the etiopathogenesis of DM in dogs and cats enable intervention at early stages leading to slowing progression, avoiding insulin dependence or even preventing DM altogether?

### How Do Past and Current Classification Systems Apply to DM in Dogs?

An exact definition of DM in dogs has not been agreed upon and also is made difficult by the many different biochemical analyzers and glucometers used in veterinary medicine. These same issues however have not prevented a reasonable and accepted compromise definition in human diabetology. We therefore suggest that overt DM in dogs be defined based on persistently increased fasting BG (for example >144 mg/dL [8 mmol/L]). The cutoff itself is arbitrary (a deviation by 1 mmol/L from the cutoff in people) and is meant simply as a tool for standardization. As was the case in people, we expect any suggested cutoff to be refined and redefined as new data from future research become available. Colleagues are encouraged to support and adopt this definition, or to propose a superior definition. Simply maintaining the current status quo (ie, absence of an exact definition) limits advancement in the field.

### T1DM: Does Autoimmunity Cause Adult-Onset DM in Dogs?

Diabetes mellitus in dogs is commonly characterized by permanent hypoinsulinemia, no increase in c-peptide in response to insulin secretagogues, and an absolute requirement for exogenous insulin administration to avoid ketoacidosis.<sup>22</sup> This presentation is consistent with T1DM, but can also occur with most other types of DM, depending on the stage of disease and severity of glucotoxicity. Glucotoxicity refers to structural and functional damage in pancreatic  $\beta$ -cells and the target tissues of insulin caused by chronic hyperglycemia. This phenomenon was demonstrated in human and rodent models and most recently in cats.<sup>23</sup> Dogs are also sensitive to glucotoxicity and in its presence can become hypoinsulinemic and diabetic despite having  $\beta$ -cell mass that previously was sufficient to maintain euglycemia.<sup>24,25</sup> Fortunately, the detrimental effects of glucotoxicity on  $\beta$ -cell function are reversible in the early stages with aggressive treatment to normalize BG. Thus, in a dog that is presented for clinical DM, the assumption that the dog is suffering from end-stage T1DM (an irreversible IDDM state) can result in a missed opportunity to treat and reverse glucotoxicity. This could be important, for example, in dogs presented for acute pancreatitis and no previous history of DM. If glucotoxicity is part of the pathology, aggressive treatment of DM within a few weeks after diagnosis could lead to sufficient recovery of  $\beta$ -cell function. However, if an assumption is made that DM in this dog is T1DM (and not DM secondary to disease of the exocrine pancreas) then it is also assumed that this dog is at an end stage of DM, and the dog would be treated with the current standard of care: Controlling clinical signs without attempting to achieve persistent euglycemia. This approach represents a self-fulfilling prophecy in that less than complete restoration of euglycemia will cause permanent damage to  $\beta$ -cells and lead to an irreversible DM state. This example illustrates the flaws of this definition of T1DM and why it is important to search for a specific etiology. Importantly, the hallmarks of T1DM in people are not present in the majority of dogs with DM.

### Serologic and Histologic Evidence of Autoimmunity

There is evidence of cell-mediated autoimmune destruction of  $\beta$ -cells in up to 50% of diabetic dogs<sup>26–30</sup> in some studies whereas others have found no evidence of autoimmune destruction.<sup>31–35</sup> In a study evaluating serum from 48 dogs with recently diagnosed but untreated DM, autoantibodies reactive against the cytoplasmic content of normal canine islet cells were not detectable in any sample.<sup>32</sup> Similarly, a recent study found no evidence of islet cell autoimmunity in 121 diabetic dogs of 40 different breeds.<sup>34</sup> Only 5 dogs were evaluated histologically, but none had lymphocytic (or other) inflammation in the pancreatic islets. In an earlier study, infiltrating mononuclear cells (predominantly lymphocytes) were observed in 6 of 18 dogs (33%) with

DM whereas in 5 dogs (28%), extensive pancreatic damage appeared to be responsible for the development of DM.<sup>28</sup> An absence or decreased numbers of islets together with degeneration and vacuolization but no inflammation was described in 3 studies evaluating pancreatic histopathology in a total of 74 diabetic dogs.<sup>31,33,35</sup>

A complicating factor in determining the prevalence of autoimmune DM is that the presence of autoantibodies and an inflammatory infiltrate depends on the residual insulin content of the cells. Insulinitis rarely is detected once  $\beta$ -cells become insulin deficient.<sup>36</sup> Therefore, a plausible explanation for the relative lack of evidence for autoimmunity in diabetic dogs could be that most studies were performed using sera or tissue at a late stage in the process when the insulin content of the islets is too low for the immune system to amount a detectable response. To date however, evidence supporting autoimmunity as a cause of DM in dogs is weak.

#### *Genetic Evidence of Autoimmunity*

DM in dogs is thought to be similar to T1DM based on identification of specific susceptibility and protective major histocompatibility complex haplotypes.<sup>37</sup> Dog leukocyte antigen (DLA) haplotypes have been identified that are more prevalent in breeds with a higher risk for DM, such as the Samoyed, Tibetan terrier, and Cairn terrier. Within breeds, however, these haplotypes are common not only in diabetic dogs but, also in controls. Other immune system genes associated with T1DM in humans also have been implicated in canine DM. Risk or protective variants have been identified in *IL-4* and other interleukin genes, *PTPN22*, *CTLA4*, and *INS*. However, these data should be interpreted cautiously because candidate gene approaches are associated with a high risk of false positives in dogs. The *DLA* locus can be particularly susceptible to false associations as a consequence of overrepresentation of genetic material from popular sires, high levels of inbreeding, or genetic drift.<sup>34,38,39</sup> In conclusion, although a compelling body of genetic studies has accumulated thus far, additional studies are necessary to determine exactly how much the DLA locus and the other aforementioned genes contribute to risk for T1DM in dogs.

Based on the above studies, most diabetic dogs have etiologies other than immune-mediated T1DM. What, then, are the most likely causative factors of DM in dogs?

#### **T2DM in Dogs**

Despite the increasing prevalence of obesity in dogs, there is no evidence that insulin resistance unmasks  $\beta$ -cell dysfunction with resulting DM as is the case in people. Obese dogs show evidence of insulin resistance but compensate appropriately through increased insulin secretion.<sup>40</sup> Even after years of obesity-induced insulin resistance, DM does not appear to develop and most obese dogs maintain euglycemia.

#### **Genetic Defects of the $\beta$ -cells Or Insulin Action**

Strong breed predispositions for DM have been reported in dogs and support a heritable component to the disease.<sup>39,41–43</sup> As described above, immune system genes might play a role, but undiscovered genetic causes of DM in dogs remain. To our knowledge, primary susceptibility genes for MODY in people have not been evaluated in dogs. A genome-wide study identified a chromosomal locus associated with serum fructosamine concentrations in Belgian Shepherds.<sup>44</sup> A causative mutation was not discovered, but positional genes involved in glucose metabolism and insulin signaling (*GAPDH* and *LETM*) were implicated.

Several of the canine breeds reported to be at increased risk for DM also are at high risk for other predisposing conditions. For example, Yorkshire terriers, Fox terriers, and Miniature schnauzers are predisposed to DM and also are at risk for pancreatitis.<sup>45,46</sup> Miniature Schnauzers also are prone to familial hyperlipidemia,<sup>47</sup> which could contribute to the breed's DM risk either directly or by the effect of hyperlipidemia on pancreatitis risk. In conclusion, although genetic predisposition is likely an important factor in DM in dogs, these studies do not lend support for one specific etiology, but rather suggest that DM in dogs comprises heterogeneous disorders.

#### **DM Secondary to Diseases of the Exocrine Pancreas in Dogs**

As in people, an association between pancreatitis and DM might exist in dogs.<sup>46,48–51</sup> In one histopathologic study, approximately 33% of diabetic dogs had evidence of concurrent pancreatitis.<sup>28</sup> In another study, histopathologic evidence of chronic pancreatitis was found in 6 of 18 diabetic dogs and acute pancreatitis was found in 5 of 18.<sup>33</sup> In contrast, other studies on diabetic dogs have found histopathologic evidence of pancreatitis to be lacking or rare.<sup>31,35</sup> In both dogs and people, it is difficult to identify a cause and effect relationship between DM and pancreatitis, and both could result from the same primary disease process. Human patients with T2DM have 1.5–1.8 fold increased risk of developing acute pancreatitis,<sup>52,53</sup> and both insulin resistance and hyperglycemia might be key factors in this process.<sup>54</sup>

Mild hyperglycemia occurs frequently in nondiabetic people suffering from pancreatitis. This observation previously was considered unimportant because hyperglycemia normalizes after pancreatitis subsides. Recently, however, a higher risk (2.7-fold) of developing prediabetes and DM within 5 years was demonstrated in previously nondiabetic people who have suffered an episode of acute pancreatitis.<sup>55</sup> In dogs, insulin secretion (assessed by glucagon stimulation) was impaired in 5 of 6 dogs with pancreatitis despite being euglycemic before stimulation.<sup>56</sup>

#### **DM Secondary to Endocrinopathies and Gestational DM in Dogs**

In contrast to Gestational DM in people, there is no evidence in dogs that developing overt DM during



pregnancy increases risk for complications in the bitch or pups. As in people, gestation is associated with increased insulin resistance in the bitch, but the mechanism is different. In dogs, progesterone stimulates the mammary gland to produce growth hormone (GH) and release it into the systemic circulation. Increased GH leads to insulin resistance.<sup>57</sup> The term Gestational DM probably is inappropriate in dogs. Regardless of source and timing, increased exposure to progesterone in the dog leads to increased GH secretion in the mammary glands whether during gestation, diestrus, or as a consequence of exogenous administration of progestins.<sup>24,57,58</sup> Therefore, the term progesterone-controlled GH overproduction DM (PGHDM) might be more appropriate,<sup>58</sup> and this disorder should be classified as DM secondary to an endocrinopathy. Also, in contrast to Gestational DM in people, there is limited evidence in dogs that underlying  $\beta$ -cell dysfunction is present before gestation. Rather, increased GH might result in such extreme insulin resistance that it alone causes DM.

It is unknown whether PGHDM dogs that go into remission remain at high risk for developing future DM independently of subsequent exposure to progesterone (suggesting that  $\beta$ -cell disease was present before exposure). However, dogs that go into remission at the end of diestrus and that are not spayed are likely to become overt diabetics during future cycles.<sup>24</sup> Also unknown is the risk that repeat exposure to high GH through estrous cycles confers on future development of DM in dogs. In 1 study that prospectively assessed 84 nondiabetic intact female dogs, only 1 dog developed DM after 2 years and no conclusions could be drawn regarding the risk conferred by increased concentrations of GH, IGF-1, and markers of insulin resistance on the development of DM.<sup>57</sup>

#### ***DM Secondary to Hypercortisolism in Dogs***

Glucocorticoids cause insulin resistance, but they also affect  $\beta$ -cell function by decreasing insulin secretion, blunting the incretin effect and by direct cytotoxicity.<sup>59–62</sup> In one study, only 8% of dogs with hypercortisolism had overt DM by traditional criteria, but 38% of dogs had moderate hyperglycemia<sup>63</sup> and would have been classified as having DM based on the criteria suggested above. Similar to PGHDM, it is unknown why some dogs with hypercortisolism develop DM and others do not. Does the difference lie in severity of or sensitivity to hypercortisolism, or does it lie in a primary pancreatic lesion that prevents adequate compensation for insulin resistance caused by glucocorticoids? If hypercortisolism merely exposes a pre-existing pancreatic lesion (caused by any one of the other etiologies of DM) in these dogs, then the prevalence of DM in dogs with hypercortisolism should be much more similar to the prevalence of DM in the general population.<sup>41,63</sup> However, it is possible that hypercortisolism merely exposes a pre-existing pancreatic lesion that would have otherwise remained subclinical.

#### **The Importance of Early and Accurate Diagnosis of Mature-Onset DM in Dogs**

Accurate diagnosis early in the course of a disease can be important in slowing or preventing progression of the disease. Immune modulation in T1DM before extensive loss of  $\beta$ -cell mass could become a viable preventive strategy in the near future, but it would require accurate classification and early diagnosis of DM.<sup>5</sup> Strategies for early detection of  $\beta$ -cell loss in humans with T1DM (before detection of glucose intolerance) are being developed.<sup>64</sup>

Exclusion of an autoimmune process in a patient with DM and concurrent (or resultant) pancreatitis might have clinical relevance in the early management. The pancreatic inflammatory process combined with transient glucotoxicity could perpetuate injury to  $\beta$ -cells and cause permanent damage. Therefore, it might be possible to prevent establishment of permanent DM in some dogs by glycemic normalization near the time of diagnosis.

Accurate diagnosis also could affect treatment strategies in the established diabetic patient. Most importantly, the risk of life-threatening hypoglycemia might be different in animals with an isolated disease of pancreatic  $\beta$ -cells (as in T1DM) as compared to animals with a disease process involving other cell types in the islets of Langerhans (as in DM secondary to diseases of the exocrine pancreas). Decreased glucagon secretion from damaged, dysfunctional, or absent  $\alpha$ -cells would increase susceptibility to exogenous insulin overdosage and might necessitate a more conservative approach to treatment. Alternatively, pancreatic polypeptide (PP) deficiency might affect hepatic sensitivity to insulin. In dogs, the liver is a primary site for developing insulin resistance,<sup>65</sup> and PP increases hepatic insulin sensitivity.<sup>66,67</sup> Pancreatic polypeptide deficiency has been identified in people with chronic pancreatitis and in rodent models, and could contribute to the development of DM.<sup>67</sup> Identifying this deficiency in a diabetic patient could have implications for treatment such preference for a “hepato-selective” insulin formulation (eg, insulin detemir).<sup>68</sup> In the few studies that have described the histopathologic abnormalities in the pancreatic islets of DM dogs, a decreased number of  $\beta$ -cells paralleled a reduction in other cell types in the islets; a complete absence of islets was frequently reported but a detailed characterization of all cell types in the islets was not performed.<sup>28,31,33</sup> Further scrutiny of the distribution of different islet cell types and the involvement of islet-produced hormones (eg, glucagon) in various types of DM in dogs is necessary.

In dogs treated for pituitary-dependent hypercortisolism with retinoic acid, the rate of progression from IFG (105–168 mg/dL [5.8–9.3 mmol/L]) to DM (BG > 168 mg/dL [9.3 mmol/L]) was significantly lower in those additionally treated with a low dosage of insulin detemir (0.1 U/kg q24h) as compared to those not treated with insulin.<sup>63</sup> This study lends support to the hypothesis that defining and treating subclinical dysglycemia could delay or prevent overt DM in dogs. It

also suggests that low doses of insulin detemir are useful and safe in regulating glycemia in dogs with only mildly increased BG. Another potential safe and effective treatment strategy could be the use of glucagon-like peptide-1 (GLP-1)-receptor agonists. The GLP-1-receptor agonists effectively maintain a noninsulin-dependent state in people with DM and have been shown to protect  $\beta$ -cells from cytotoxicity caused by glucocorticoids.<sup>60</sup>

### Juvenile-Onset DM in Dogs

Reports of DM in young dogs are uncommon.<sup>69–76</sup> Most reports describe insulin-dependent dogs with various histopathologic abnormalities of the pancreas, but no clear etiology. Similar to neonatal DM in humans, none of the reported cases of juvenile-onset DM in dogs were thought to be immune-mediated based on histopathology. Pancreatic islet lesions described include atrophy, aplasia, or hypoplasia, or inflammation of the exocrine pancreas. Congenital hypoplasia of islet  $\beta$ -cells has been described in Keeshond puppies, but solitary  $\beta$ -cells still were present.<sup>72</sup> Similar findings were described in a Chow and a Brittany Spaniel.<sup>70,74</sup> In the diabetic Keeshond, insulin concentration in the pancreas was markedly decreased, and glucagon concentration also was decreased (approximately 33% of normal). Despite this finding, glucagon response to arginine was normal.<sup>72</sup> DM inheritance was suspected to be autosomal recessive, but no specific genetic mutation was identified.<sup>71</sup> In young Greyhounds, German Shepherds and Golden Retrievers, DM has been associated with atrophy of the exocrine pancreas<sup>70,73</sup> and exocrine pancreatic insufficiency.<sup>75,76</sup>

As discussed above, mutations in genes encoding the  $K_{ATP}$  channel are the most common cause of neonatal DM in people, and these patients can be treated with sulfonylurea orally. Limited data are available to support monogenic causes of DM in dogs, and possibly a subset of diabetic puppies suffer from mutations similar to those described in humans. Such puppies could become insulin-independent with proper treatment selected based on the specific genetic etiology. One veterinary report indicated that no mutations were found in the human neonatal DM susceptibility gene *KCNJ11* in dogs, but the data itself were not presented.<sup>43</sup>

### Prediabetes in Dogs

Currently, there is no established definition for the diagnosis of prediabetes in dogs, and no prospective studies have demonstrated the utility of any diagnostic test in predicting the development of diabetes. As mentioned above, biomarkers for detection of  $\beta$ -cell death are being developed and might aid in early detection of T1DM in dogs. Abnormal insulin secretory response to glucagon stimulation (as detected in patients with pancreatitis)<sup>56</sup> might prove to be a marker of prediabetes in dogs but must be confirmed with prospective studies. Validation of PO or IV glucose tolerance tests in dogs could also facilitate a diagnosis of prediabetes.

## DM in Cats: Breaking Down the Type 2 Umbrella

Specific criteria for a diagnosis of DM in cats have not been agreed upon, in part for similar reasons as explained above for dogs, but with the additional difficulty caused by the prevalence of stress hyperglycemia in cats. To enable clinicians and researchers to better compare study and treatment results in the future, we propose that DM in the cat be more clearly defined. Importantly, an RI study of serum fructosamine in cats should be performed, generating separate RIs for male and female cats, and standardization across laboratories should be attempted.<sup>77</sup> Alternatively, a similar approach could be considered but with a feline glycosylated hemoglobin assay. These steps would allow incorporation of serum fructosamine or glycosylated hemoglobin into the definition of prediabetes, subclinical DM, and overt DM in cats. Without an accurate indicator of long-term glycemia (fructosamine or glycosylated hemoglobin), it is difficult to recommend a new definition that encompasses all of these stages. Although there are no comprehensive RI studies for BG in cats, multiple studies in adult healthy cats consistently show fasting BG do not exceed 126 mg/dL (7 mmol/L).<sup>78–83</sup> Thus, we propose that overt DM in cats be defined as documentation of a persistently increased fasting BG  $\geq$  126 mg/dL (7 mmol/L), supported by documentation of elevated fructosamine or glycosylated hemoglobin, regardless of clinical signs attributable to a pathologic excess of circulating glucose.

Based on clinical presentation, epidemiology, genetic research and association with islet amyloid deposits, DM in cats previously has been classified as a T2DM.<sup>22,84</sup> As in T2DM in people, obesity and physical inactivity are major risk factors for DM in cats.<sup>85,86</sup> Also similar to T2DM in people is the age of disease onset (diabetic cats often are older) and the potential for insulin independence. Based on these features and because T2DM is an umbrella term that includes unknown etiologies, type 2 indeed might be an appropriate category for most diabetic cats. However, when a disease such as hypersomatotropism is present, by definition T2DM is excluded, and DM should be classified as “secondary to an endocrinopathy”.

From a clinical perspective, therapy and remission rates differ between T2DM and DM secondary to endocrinopathies, and from a research perspective, differentiating between these types of DM might help with the discovery of underlying etiologies for T2DM. Also, as mentioned above, a precise diagnosis early in the course of the disease might be important in preventing or slowing progression.

### T1DM in Cats

Significant lymphocytic infiltration of the endocrine pancreas, as evidence of cell-mediated autoimmune destruction of  $\beta$ -cells, has been reported in only a handful of diabetic cats. Also, there are no reports of naturally occurring insulin or  $\beta$ -cells autoantibodies in



cats. Thus, if T1DM occurs in cats it is probably rare.<sup>22</sup>

### DM Secondary to Diseases of the Exocrine Pancreas in Cats

Diabetes mellitus in cats often is associated with abnormalities in serum markers of exocrine pancreatic disease.<sup>87–89</sup> A weak positive correlation between feline pancreatic lipase activity (fPLI) and serum fructosamine was reported in cats with DM, suggesting that subclinical pancreatitis might cause inadequate glycemic control.<sup>88</sup> Alternatively, inadequate glycemic control (reflected by increased serum fructosamine) might cause ongoing damage to the exocrine pancreas (reflected by increased fPLI), as suggested by an experimental study in which pancreatic neutrophils increased in healthy cats with experimentally induced hyperglycemia.<sup>90</sup> The fact that most diabetic cats with increased fPLI do not have gastrointestinal signs and are not less likely to achieve remission further argues in favor of inadequate glycemic control as the cause of increased fPLI.<sup>88,89,91</sup> Similarly, T2DM in people is considered a risk factor for pancreatitis.<sup>52–54</sup> In contrast, based on histopathology, the frequency of pancreatitis is similar in diabetic cats and control cats suggesting no cause and effect.<sup>87,92–94</sup> Therefore, the majority of evidence (from feline and human clinical and experimental models) points to DM being the cause rather than the result of the abnormalities in the exocrine pancreas. The possibility that in some cats pancreatic disease causes DM cannot be excluded, but this outcome seems relatively uncommon.

### DM Secondary to Endocrinopathies in Cats

Several endocrinopathies have been associated with DM in cats. The most important are hypersomatotropism (excess production of growth hormone usually caused by a benign tumor of somatotrophs of anterior pituitary gland) and hypercortisolism (cortisol excess from an adrenal or pituitary tumor, or iatrogenic). Naturally occurring hypercortisolism is rare in cats. In contrast, hypersomatotropism-induced DM is common. Recently, 1,221 diabetic cats were screened in first opinion practices in the United Kingdom and 26% were found to have serum insulin-like growth factor-1 concentrations (IGF-1) > 1,000 ng/mL.<sup>95</sup> Of these cats, 63 (20%) were further evaluated, including intracranial imaging, postmortem evaluation, or both. Based on these 63 cats, IGF-1 had a positive predictive value of 95%, confirming the prevalence of hypersomatotropism among UK diabetic cats to be 25%.<sup>95</sup> Interestingly, only 1 in 4 attending clinicians originally strongly suspected hypersomatotropism in cats subsequently diagnosed with the disease, suggesting that many affected cats present with DM but otherwise lack readily identifiable signs of acromegaly. The investigators suggested use of the term hypersomatotropism over acromegaly because the latter implies the presence of physical features indicative of GH excess.<sup>95</sup>

Because of the high prevalence of hypersomatotropism in cats with DM, routine measurement of IGF-1 is recommended, regardless of clinical presentation. This practice is especially important because timely diagnosis might have major impact on the understanding of an individual cat's DM, ideal treatment modalities and ultimate outcome. Treatment with the somatostatin analogue pasireotide<sup>96</sup>, radiotherapy<sup>97</sup> or hypophysectomy<sup>98</sup> has shown that when the underlying GH excess is properly managed, glycemic control can improve dramatically. Diabetic remission rates as high as 85% have been achieved in diabetic cats with hypersomatotropism treated by hypophysectomy.<sup>98</sup> Such high remission rates, even in cats that have been diabetic for several years, suggest that diabetic cats with hypersomatotropism might not suffer from intrinsic  $\beta$ -cell pathology. Nevertheless, early treatment of hypersomatotropism is prudent considering the inevitable and ultimately negative sequelae of glucotoxicity on the  $\beta$ -cells. High rates of DM remission in treated hypersomatotropism also are indirect evidence of intrinsic  $\beta$ -cells pathology in diabetic cats without hypersomatotropism. In such cats, with current treatment recommendations remission rates usually are much lower and remission is only temporary in approximately 30% of cases.<sup>82,99</sup>

Secondary DM occurs in approximately 80% of cats with spontaneous hypercortisolism (in contrast to only 8% in dogs).<sup>64,97</sup> Additionally, previous exogenous exposure to glucocorticoids is a risk factor for DM in cats. Increased insulin resistance from glucocorticoid excess could cause cats with subclinical DM to progress to an overt stage. Most cats treated with high dosages of glucocorticoids do not develop DM, supporting the theory of a pre-existing subclinical DM state in those cats that do develop glucocorticoid-induced DM. On the other hand, diabetic cats with a previous history of glucocorticoid administration are more likely to achieve diabetic remission.<sup>99</sup> Additional research is needed to clarify the relationship between glucocorticoids and DM in the cat.

### Prediabetes in Cats

Currently, there are no established definitions for the diagnosis of prediabetes in cats. Despite the association of DM with obesity in cats, obesity cannot be used as a criterion for diagnosis of prediabetes because most obese cats do not develop DM. Additional mechanisms must be necessary for obese cats to become diabetic. For example, a melanocortin receptor-4 polymorphism is overrepresented in obese compared to lean diabetic cats and could be a contributing risk factor.<sup>100</sup> In people, although obesity is considered a primary risk factor for T2DM, its presence is only useful in first-line screening for prediabetes and it is not effective as the sole screening metric. This is because obesity reflects insulin resistance, which in itself does not lead to DM unless pancreatic dysfunction also is present. In contrast, prediabetes implies pancreatic dysfunction, with or without insulin resistance.

Surrogate markers of pancreatic dysfunction that assess glucose tolerance (eg, fasting BG, glucose

tolerance tests, glycosylated hemoglobin, fructosamine) are better predictors of progression to DM than measures of obesity and insulin resistance, and are used to screen people (eg, obese, pregnant) at risk for DM.<sup>1</sup> None of these surrogate markers exclusively reflects  $\beta$ -cell dysfunction, and none indicates an irreversible disease process. Therefore, these markers are not 100% predictive. Glucose intolerance might be a reflection of insulin resistance,  $\beta$ -cell dysfunction, or often, a combination of both.

Several studies report on glucose intolerance in cats as demonstrated by IV and PO administration of glucose.<sup>79,80,101</sup> In general, these studies have identified abnormalities in overweight and obese cats, although abnormalities in lean cats also have been detected. Nevertheless, no prospective longitudinal studies have determined the utility of any diagnostic test in predicting the development of overt DM in cats. Studies on glucose intolerance in cats leave 2 clinically relevant questions unanswered: 1. Assuming prediabetes can be characterized by glucose intolerance, is this glucose intolerance predictive of development of DM? and 2. Is the diagnosis of glucose intolerance more predictive of developing DM than other more easily measurable parameters such as body weight, body condition score, or body mass index?

To be predictive of DM, a diagnosis of prediabetes should detect subclinical  $\beta$ -cell pathology and not be made based on tests that merely reflect the normal physiology of the cat. The glucose intolerance identified in some studies might not represent pathology but rather a normal response to a supra-physiologic glucose load. The response often is wrongly considered pathologic because of extrapolation from the normal response in other species, particularly humans. Cats are obligate carnivores and have evolved to handle glucose differently than the omnivorous animal models (eg, human, dog, mouse). For example, cats cannot sense dietary sugars because of mutations in *Tas1r2*, the gene that encodes a subunit of the sweet receptor.<sup>102</sup> If the ability to sense glucose (which is important in glucose regulation in other species) is used as a test to identify glucose intolerance, all cats will fail the test. Clearly, such a test has no predictive value for the diagnosis of DM in cats. Similarly, when glucose is administered PO in tolerance tests, the ability of the normal cat to handle a glucose load should be taken into account. When glucose is added to a high-protein diet at 2 g/kg, prolonged and excessive hyperglycemia (>180 mg/dL [10 mmol/L]) occurs in healthy cats.<sup>103</sup> However, this outcome is expected because healthy cats, in contrast to dogs and people, do not secrete the incretin hormone GIP (glucose-dependent insulinotropic peptide) in response to orally administered glucose.<sup>78,104</sup> Therefore, this so-called "glucose intolerance" is a normal response and unlikely to be predictive of prediabetes.

Glucose intolerance as measured by abnormal hyperglycemia after PO administration of glucose was demonstrated in obese (compared to lean) cats with 2 g/kg glucose (administered via gastric intubation). Whether this was the result of insulin resistance

exclusively or also the result of  $\beta$ -cell dysfunction was not elucidated.<sup>80</sup> Decreased GLP-1 concentrations also were reported in the obese cats, consistent with changes seen in diabetic people. However, GLP-1 secretion could not be assessed accurately in that study because of methodologic problems in its measurement.<sup>105</sup> Importantly, even if the PO administration of glucose at this high dosage is a useful test to predict DM, it is unlikely to be clinically applicable because of the need for gastric intubation as well as the high frequency of adverse effects such as vomiting and diarrhea.<sup>80</sup>

Incretin hormones have a central role in the pathophysiology and early detection of DM.<sup>106</sup> Intravenous glucose tolerance tests (IVGTT) are therefore inferior to oral glucose tolerance test because they do not assess the incretin effect. Glucose intolerance as measured by IVGTT has been detected in obese cats.<sup>79,101</sup> Insulin concentrations during the first 10 minutes of the IVGTT are dependent almost entirely on  $\beta$ -cell function. Blunting of this "first phase" insulin response (FPIR) in people is characteristic of prediabetes and DM but this blunted FPIR is not seen in nondiabetic obese subjects.<sup>7</sup> In cats, lean and obese, FPIR is decreased or absent relative to the response seen in people.<sup>79,101,107,108</sup> This could be the result of a relatively low sensitivity of  $\beta$ -cells to glucose stimulation in cats when compared to people.<sup>109</sup> In 2 studies, there was a trend in obese cats toward lower or even absent FPIR compared to lean cats, suggesting that, with obesity,  $\beta$ -cell function decreases in cats.<sup>79,101</sup> Neither of these studies followed the obese cats to determine if they later developed DM.

In summary, the lack of GIP response to PO glucose, decreased sensitivity to an acute increase in BG (blunted FPIR) and other physiologic peculiarities, contribute to the cat's inability to handle large glucose loads (whether IV or PO) and cause the appearance of "glucose intolerance". This could limit the usefulness of these tests in our efforts to define and diagnose prediabetes in cats as in terms of differentiating individuals at high risk of progression to overt DM as compared to individuals not at high risk.

In the past few years, HbA<sub>1c</sub> has been employed as a screening methodology for prediabetes in people. There is no specific cutoff for the presence of prediabetes, but rather the higher the HbA<sub>1c</sub>, the greater the risk of DM. Glycosylated hemoglobin or serum fructosamine or both might be useful in cats, as they are in people, as predictors of DM. It remains to be determined however whether these parameters are sensitive enough for this purpose. In a study of nondiabetic cats that were infused with dextrose for several weeks, mild hyperglycemia resulted in a noticeable increase in serum fructosamine from the middle of the reference range to the upper end of the reference range used in that study.<sup>110</sup> As mentioned before, there is no well-established RI for serum fructosamine in cats<sup>77</sup> and laboratory methods vary across institutions. Furthermore, no longitudinal studies have evaluated the utility of serum fructosamine in predicting DM. In another study of nondiabetic cats (all with serum fructosamine within the reported normal

range), a weak but significant correlation was found between serum fructosamine and body weight, and male cats had higher serum fructosamine than did female cats (even after adjusting for body weight differences).<sup>77</sup> Overweight male cats are at high risk of developing DM,<sup>111</sup> and higher serum fructosamine in these cats could be the result of a subgroup being prediabetic and having less than ideal glycemic control. Whether or not this is true needs to be determined in follow-up studies.

### Final Remarks

Classification of DM in humans has been refined substantially over the past decade and has required clinicians and researchers to take into account the diversity of underlying disease processes that are being grouped under the broad umbrella term of DM. This proactive approach toward better understanding of the different types of DM has decreased the number of misdiagnoses, and most importantly, enabled the adoption of the most appropriate treatment modalities specifically suited to the particular underlying disease process. A uniformly accepted classification system has been lacking in veterinary medicine, as have specific definitions of companion animal DM itself and the concept of prediabetes in companion animals. We hope this review stimulates work toward adopting a similar classification system in veterinary medicine, based on increasing knowledge of the underlying disease mechanisms. We also hope the suggested adaptation of the ADA system soon will become outdated, reflecting increased understanding of DM in companion animals. Such increased understanding likely will lead to better treatment practices, higher remission rates, and, ultimately increased animal welfare.

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