Diabetes mellitus is an endocrine disorder characterized by insufficient production of insulin in the body (type 1, or insulin-dependent, diabetes) or a resistance to the hormone itself (type 2 diabetes).

Dogs typically develop type I diabetes. Other forms of diabetes mellitus in dogs include gestational diabetes and forms resulting from a variety of disorders and/or drugs. Achieving remission in the latter patients is extremely rare, even with correction of the underlying problem.

Treatment of diabetes mellitus can pose many challenges, depending on the type and degree of involvement. Presenting clinical signs for patients with diabetes mellitus commonly include polyuria and polydipsia (PU/PD). Additional signs can include lethargy, weight loss, and increased appetite, the degrees of which depend on the duration of disease and whether diabetes mellitus is the sole disorder or if additional disease processes are involved. Diabetes mellitus tends to be diagnosed most often in middle-aged to older dogs, with overweight, intact females at greatest risk.

PATHOPHYSIOLOGY

The pancreas is an organ with both exocrine and endocrine functions.

Exocrine Function

The exocrine aspect of the pancreas aids in digestion and absorption of nutrients, including glucose, by releasing a variety of enzymes through the pancreatic duct. Glucose is absorbed through the small intestine with the aid of a cotransporter across the intestinal membrane, where a cascade of physiologic sequences continues the transport until the glucose molecule reaches the blood supply. Once in the blood, glucose is either utilized for energy production or stored as glycogen in the liver or skeletal muscles for later use. This normal process of postprandial (after eating) glucose storage prevents blood glucose surges, helping to maintain a normal physiologic state.

Endocrine Function

During and after intestinal absorption of glucose and other nutrients into the blood supply, the endocrine aspect of the pancreas becomes active as groups of cells, called islets of Langerhans, synthesize and secrete hormones that are released directly into the blood supply. These hormones are used for maintaining glucose homeostasis. Most notable are insulin and glucagon, derived from beta and alpha cells, respectively. These 2 hormones have an inverse relationship: when blood glucose levels are elevated, insulin is secreted, and when blood glucose levels are low, glucagon is secreted. Insulin receptors are found on all cell membranes throughout the body; therefore, when insulin is released into the blood (in response to increasing levels of glucose), it stimulates the uptake, utilization, and storage of glucose in tissues, as well as amino acid uptake and synthesis of fatty acids. As glucose
levels decline, glucagon counters the effects of insulin by increasing blood glucose. Glucagon’s effect is mainly at the level of the liver, stimulating glycogenolysis (the process by which glycogen is converted to glucose), and gluconeogenesis (the process by which noncarbohydrate sources are broken down into glucose). However, glucagon’s physiologic role is much more complex. Insulin and glucagon work synergistically to maintain glucose homeostasis.

**Development of Diabetes**

The development of diabetes mellitus can be multifactorial. For example, it can occur secondary to the loss of beta cell function and subsequent lack of insulin production, and/or it can be associated with insulin antagonism for a variety of reasons. Predisposing factors include immune-mediated beta cell destruction, chronic pancreatitis, and obesity, as well as other diseases or infections that can cause insulin antagonism. By the time diabetes mellitus is diagnosed, the resultant chronic state of hyperglycemia has usually already caused irreversible damage to the pancreatic beta cells. Therefore, dogs, except for very rare exceptions, always have insufficient insulin production (type I diabetes), with twice-daily injections of insulin required for optimal management.

Considering the many conditions that can be associated with diabetes mellitus, it may be necessary to screen for complicating factors that can pose challenges to successful management (BOX 1).

**CLINICOPATHOLOGIC ASSESSMENT**

Patients with diabetes mellitus usually present with PU/PD, lethargy, polyphagia, and weight loss, with PU/PD as the primary clinical sign.

**Polyuria and Polydipsia**

With chronic hyperglycemia, the number of glucose molecules within the proximal renal tubules exceeds the capacity of the available transport molecules to remove them. The resulting retention of glucose in the renal tubules increases the osmotic gradient. Water reabsorption becomes compromised, and water begins to follow the higher concentration of glucose into the urine, resulting in polyuria. This is called osmotic diuresis secondary to exceeding the overall renal threshold of glucose (>180 mg/dL). The consequence of osmotic diuresis is polydipsia, a compensatory mechanism to help prevent dehydration.

**Laboratory Analysis**

In patients with uncomplicated diabetes mellitus, serum biochemical profile analysis reveals hyperglycemia, with the remaining profile typically unremarkable. Urinalysis results
include glucosuria due to blood glucose levels exceeding the proximal renal tubular threshold for reabsorption.

Additional abnormal urinalysis results may include altered urine pH and proteinuria, depending on whether a urinary tract infection is present. Other parameters tend to be unremarkable; white blood cell count, urine specific gravity (USG), and urobinogen and nitrite levels are unreliable when dry chemistry analysis (i.e., reagent strip) is used. If USG is evaluated using a refractometer, the result is typically between 1.025 and 1.035. This mildly reduced range (concentrated range, >1.030) is due in part to effects of osmotic diuresis and subsequent polydipsia resulting in urine dilution, but despite the severity of PU/PD, the value remains higher than expected due to the presence of glucose molecules. These molecules can increase USG by 0.008 to 0.010. USG values <1.020 may indicate a concurrent disease process.

**Polyphagia**

Polyphagia results from the patient being nutritionally compromised, with loss of lean body mass due to loss of lean body mass from loss of muscle proteins as a result of muscle starvation.

**BOX 1 Diabetic Ketoacidosis**

Diabetes mellitus can become “complicated” and lead to a state called diabetic ketoacidosis (DKA). This usually occurs if a secondary disease process is present, such as chronic pancreatitis, or if diagnosis of diabetes mellitus is delayed, resulting in a long-term increase in plasma glucose levels.

Other metabolic and chronic systemic inflammatory states have also been associated with progression of otherwise uncomplicated diabetes mellitus into DKA. For instance, obesity is an area of interest with regard to the inflammatory cytokines produced and the adverse role they play in physiologic homeostasis.

An extensive study of DKA treatment is not within the scope of this article; therefore, to briefly summarize, the goals are to:

- hospitalize the patient,
- address the physiologic derangements through the correction of hydration and acid-base imbalance, and
- correct and maintain a relatively normal blood glucose level via administration of a short-acting, regular insulin, which allows the patient to recover from its debilitated state and regain a normal appetite.

Once appetite returns to normal, the type of insulin used can be switched from regular insulin to an intermediate- or long-acting product.

**BOX 2 Questions and Considerations for Owners of Dogs with Diabetes Mellitus**

- What is the patient’s home feeding schedule?
- What diet and how much of it is fed at each meal? Are any treats given (be specific)?
- Are there other pets in the household? If so, can they be separated from the patient at meal time?
- Is the owner able to administer insulin injections? Is he or she willing to learn?
- Does the patient need to lose weight? Gain weight? Neither?
- Is the owner able to perform glucose curves at home? If so, recommend purchasing a quality glucometer that is reliable in dogs (e.g., AlphaTRAK 2).
- Explain to the owner that, during the regulation period, glucose curves will need to be performed every 7 to 10 days, either in the hospital or at home. This time period allows the body to adjust to the calculated insulin dosage and enables the clinician to determine the efficacy of the chosen dose.
- Explain that regulating diabetes mellitus is a process and that complicating factors may be involved, which may require additional diagnostics and management approaches.
**TABLE 1** Intermediate-Acting Insulins for Dogs

<table>
<thead>
<tr>
<th>INSULIN</th>
<th>ONSET OF ACTION</th>
<th>PEAK EFFECT</th>
<th>DURATION OF ACTION</th>
<th>FORMULATION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lente porcine zinc suspension</td>
<td>Immediate</td>
<td>2–10 h</td>
<td>8–20 h</td>
<td>40 U/mL</td>
<td>Same amino acid sequence as canine insulin</td>
</tr>
<tr>
<td>Neutral protamine Hagedorn (NPH)</td>
<td>0.5–3 h</td>
<td>2–8 h</td>
<td>6–18 h</td>
<td>100 U/mL</td>
<td>Recombinant human insulin</td>
</tr>
</tbody>
</table>

**INSULIN ADMINISTRATION**

**Formulations**
Exogenous insulin preparations used in dogs for long-term management include intermediate- and long-acting formulations. Each type of insulin has different handling requirements; therefore, careful attention to manufacturer recommendations is important to allow for maximum efficacy of product. For example, some formulations require gentle mixing of the insulin suspension, while others require vigorous shaking. Each insulin preparation requires a specific insulin syringe. Available formulations used in dogs are listed in **TABLES 1 AND 2**.

So which insulin type do you choose? Factors influencing selection may include the size of the dog, the clinician’s personal preference, and insulin availability and cost. There is no real right or wrong selection. Owners need to understand that one insulin type may not result in adequate regulation; therefore, the patient may need to switch formulations later.

**Administration**
Patient sensitivity to exogenous insulin is variable, as is the potency of various insulin types (e.g., insulin detemir). As a result, all patients should be started on a low dose that is increased incrementally every week until the desired glucose curve is achieved. Dosage and frequency should be determined on a case-by-case basis.

Recommended starting doses range from 0.25 to 0.5 U/kg, and are most commonly given every 12 hours with a meal. Insulin is ideally administered after a full meal is consumed. However, a dose given 10 to 15 minutes before feeding can be advantageous in certain situations because it allows timelier onset of the insulin. Caution must be exercised, though, and the patient’s eating habits must be considered when using this method because if the patient does not eat, a hypoglycemic episode can result.

**Glucose Curves**
Glucose curves should be performed to interpret the response and duration of the selected insulin type and dosage. To perform a curve, measurement of the blood glucose level every 2 hours throughout a 12-hour period is necessary. The 3 aspects of the curve are the peak, nadir, and curve level/duration between these 2 points (FIGURE 1).

A strong clinical indicator that the patient is becoming regulated is the reduction or resolution of PU/PD and a noticeable improvement in the patient’s activity level. Continued weekly glucose curves are still required to fine-tune glucose levels. The curve is different for all patients, and determining an adequate curve is based on clinical assessment and the quality of the curve.

Ultimately, the curve can help caregivers closely monitor the patient for periods of prolonged or acute
hypoglycemia, insulin resistance, and duration of insulin action and make an accurate dosage change, if needed.

**Hypoglycemia**
A hypoglycemic episode is characterized by onset of lethargy and weakness and can advance into disorientation and even seizures, depending on severity. Prompt treatment can be achieved by either feeding a meal or applying a syrup to the buccal membranes. With more advanced levels of hypoglycemia, emergency intervention using intravenous 50% dextrose may be warranted.

**Somogyi Effect**
Persistent, and even increasing, levels of hyperglycemia despite increasing insulin dosages warrant close attention to the glucose curve. The phenomenon termed the Somogyi effect results from insulin overdose and subsequent hypoglycemia (glucose <60 mg/dL). To counteract this acute hypoglycemic crisis, the sympathetic nervous system triggers a release of epinephrine and other counterregulatory hormones, which promote hepatic glycogenolysis and gluconeogenesis. They also act directly on skeletal muscles to produce lactate, which the liver converts to glucose. This response leads to an acute and rapid spike in blood glucose, which can easily be missed with routine spot glucose checks.

The Somogyi effect can be detected on a full glucose curve as a rapid drop in blood glucose, typically seen within the first few hours after insulin injection (FIGURE 2). If this phenomenon is occurring, the patient must start back at a low insulin dosage, monitored by repeated glucose curves weekly and with only small incremental increases in dosage until the desired dosage and effect are achieved. If, after full curves are performed and no drop in glucose is apparent, persistent hyperglycemia with little to no response to the exogenous insulin is seen, insulin resistance needs to be considered.

**Insulin Resistance**
Insulin resistance is defined as having a persistent blood glucose curve of >200 mg/dL at an insulin dosage greater than 1.0 to 1.5 U/kg. At this point, it is crucial to confirm that the insulin is being handled and administered correctly by the owner, that the correct insulin syringe is being used (U-40 versus U-100), and that the insulin is not outdated.

---

### TABLE 2 Long-Acting Insulins for Dogs

<table>
<thead>
<tr>
<th>INSULIN</th>
<th>FORMULATION</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin detemir(^1)</td>
<td>100 U/mL</td>
<td>Synthetic insulin analogue that binds to plasma proteins and is released slowly. Initial starting dose of 0.1 U/kg (significantly less than other insulins). Due to potency, currently only used in large dogs. Pharmacokinetics/pharmacodynamics still being evaluated in dogs.</td>
</tr>
<tr>
<td>Protamine zinc insulin (PZI)(^2)</td>
<td>40 U/mL</td>
<td>Recombinant human insulin. FDA-approved for use in cats in 2009. Recent studies support use in dogs with diabetes mellitus. Due to cost and higher dose requirements, typically not first choice for use in dogs. Previous formulations were pork/beef derived and removed from market in 2008.</td>
</tr>
</tbody>
</table>

\(^1\) Somogyi Effect
\(^2\) Insulin Resistance

---

**FIGURE 2.** The Somogyi effect is illustrated in this graph by the sharp decline in blood glucose (<60 mg/dL) between the hours of 8:00 and 10:00 AM. The body immediately responds to the crisis by releasing counterregulatory hormones, causing an acute spike in blood glucose. The patient remains persistently hyperglycemic thereafter. Without performing full glucose curves, this phenomenon can be easily missed and hyperglycemia mistaken for inadequate insulin dosing or insulin resistance.
Once this checklist is complete, exploring reasons of insulin resistance is warranted. Resistance can be secondary to a variety of disorders, such as infections (e.g., urinary tract infection), hyperadrenocorticism, pancreatitis, hypothyroidism, and obesity. Therefore, performing additional diagnostics is necessary to identify and treat the underlying cause of resistance.

Fructosamine and Urine Glucose Monitoring
Fructosamine is a glycated serum protein complex that reflects average blood glucose concentration over the previous 1 to 3 weeks. Fructosamine testing results should always be used in conjunction with full glucose curves and the clinical history to judge glycemic control. A recent study evaluating fructosamine levels in 24 canine patients with compensated (controlled) diabetes revealed that 17 had a fructosamine level >500, which is indicative of poor glycemic control.

Urine glucose monitoring in the home setting, using a urine reagent strip, may help identify persistent hypoglycemia, hyperglycemia, and/or ketonuria. This test is for screening only, and insulin adjustments should never be based on these results alone. Caution must be taken with interpreting the results of both fructosamine and urine glucose testing. However, results of these tests may indicate the necessity to perform a full glucose curve, making these tests valuable tools.

NUTRITION
There is much controversy concerning the optimal diet for a diabetic dog. Options include a high complex carbohydrate–low protein diet or a high protein–low carbohydrate diet.

The level of added fiber within such foods is still being evaluated, but studies suggest that added fiber allows for a reduction in overall calories, which translates to better glycemic control. The fat content of the diet should be based on concurrent illness and adjusted to an appropriate level. For example, a patient with diabetes mellitus and concurrent pancreatitis should be fed a diet lower in fat.

Diet Selection
There is no magic formula to determine the correct diet for a dog with diabetes mellitus. Therefore, all factors need to be considered when making a selection, such as body condition score, concurrent disease processes (e.g., pancreatitis, obesity), food palatability, food caloric density in relation to volume being fed, and cost. Overall, the most important aspect of selecting a diet is to ensure it is highly digestible, with complex carbohydrates, and—even more important—that the patient will eat it.

The ultimate goal behind diet selection is for the diet to be used synergistically with exogenous insulin to promote glycemic control, thereby avoiding glucose spikes. A diet with complex carbohydrates (e.g., fiber) promotes slower digestion and absorption of glucose and, as a result, a more constant level of blood glucose throughout the day.

As a rule, it is best to avoid semi-moist diets, as these formulations contain simple carbohydrates that influence postprandial blood glucose spikes, and the glycerol coating used to keep them moist is quickly converted to glucose once consumed. Some patients, in the author’s experience, can be very selective about their diet; therefore, compromising with the patient on diet selection may need to be considered, even if the selected diet is not ideal. TABLE 3 lists some basic considerations when choosing a diet for a diabetic dog.

<table>
<thead>
<tr>
<th>ITEM</th>
<th>CONSIDERATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Fresh water should be available at all times. Canned food is not required.</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Soluble fibers are preferred, such as fructo-oligosaccharide, inulin, pectin, and mucilage. Insoluble fibers, such as cellulose and psyllium, may help with satiety. &lt;55% dry matter carbohydrate; 7% to 18% fiber</td>
</tr>
<tr>
<td>Protein</td>
<td>Moderate to high protein content is recommended. Highly digestible (&gt;82%), high-quality protein is preferred. &lt;15% to 35% dry matter</td>
</tr>
<tr>
<td>Fat</td>
<td>Restrict if patient has history of pancreatitis or hyperlipidemia is present. &lt;25% dry matter</td>
</tr>
</tbody>
</table>
### BOX 3 Calculating RER and MER

<table>
<thead>
<tr>
<th>Patient: Schnauzer</th>
<th>Body condition score: 3/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight: 13.6 kg</td>
<td>Chosen diet: 300 kcal/cup (8 oz)</td>
</tr>
</tbody>
</table>

#### Formulas

<table>
<thead>
<tr>
<th>CALCULATION</th>
<th>FORMULA</th>
<th>PATIENT REQUIREMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. RER</td>
<td>$70 \times (BW_{0.75}^{1.75})$ or $30 \times (BW_{0.75}) + 70$</td>
<td>$70 \times (13.6)^{1.75} = 495.6$ kcal/day</td>
</tr>
<tr>
<td>2. MER</td>
<td>$1.6 \times$ RER</td>
<td>$1.6 \times 495.6 = 793$ kcal/day</td>
</tr>
<tr>
<td>3. Diet (total daily amount)</td>
<td>MER + (kcal/cup)</td>
<td>$793 + 300 = 2.6$ cups/day</td>
</tr>
<tr>
<td>4. Diet (amount/feeding)</td>
<td>(cups/day) + 2</td>
<td>$2.6$ cups/day + 2 = $1.3$ cups q12h</td>
</tr>
</tbody>
</table>

### Amount to Feed

Once a diet is selected, determination of how much of it to feed is based on the calculated daily kilocalories required to meet the patient's need to maintain, gain, or lose weight. This amount is then divided equally with each insulin injection. Ideally, the patient needs to eat its fully calculated meal with each injection every 12 hours to allow accurate evaluation of the efficacy of the administered insulin in conjunction with the selected diet.

To calculate the patient's daily kilocalorie requirement, the patient's daily resting energy requirement (RER) must first be determined. The patient's body condition score is then used to choose the appropriate energy factor needed to determine metabolic energy requirement (MER). The MER factor can range from 0.8 to 2 depending on whether the patient needs to lose, gain or maintain weight.17

Once the patient's daily kilocalorie needs are known, the selected diet can be evaluated for kilocalories per can or cup and the daily amount divided to be fed in equal amounts with each insulin injection. An example of this calculation, using approximate values, is provided in BOX 3.

### Glucose Monitoring

When the patient is on an appropriate diet, metabolic changes associated with proper nutrition may cause insulin sensitivity to increase, resulting in a drop in blood glucose. Therefore, continued monitoring of glucose every 3 to 6 months until the desired effects are achieved is recommended to avoid potential hypoglycemia.

### CONCLUSION

Diabetes mellitus is a common endocrinopathy seen in small animal practices. Upon diagnosis, it is paramount to treat this disorder promptly to avoid the debilitating metabolic disturbances that can result. How this disease develops is still not completely understood, and research on the topic continues. Regardless, it is important to recognize its clinical signs when they present and to have a working understanding of the clinicopathologic assessment process, including knowledge of how to regulate the patient and to recognize potential complications that may develop during short- and long-term treatment efforts.

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### References

CE Test Article 4 Canine Diabetes Mellitus: It’s About the Sugar

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1. Diabetes mellitus in dogs is most commonly associated with insulin resistance.
   a. True
   b. False

2. Which is the primary clinical sign associated with uncomplicated diabetes mellitus?
   a. Lethargy
   b. Polyuria and polydipsia
   c. Decreased appetite
   d. Weight gain

3. Within the islets of Langerhans, which cells synthesize and secrete insulin and glucagon, respectively?
   a. Beta cells, gamma cells
   b. Alpha cells, beta cells
   c. Delta cells, acinar cells
   d. Beta cells, alpha cells

4. The Somogyi effect is characterized by
   a. Persistent hypoglycemia
   b. Acute hypoglycemia with rebound hyperglycemia
   c. Insulin resistance
   d. None of the above

5. Management of canine diabetes mellitus requires
   a. Owner compliance
   b. Exogenous insulin therapy
   c. Client communication
   d. All of the above

6. Glucosuria occurs when blood glucose exceeds ________ mg/dL.
   a. 140
   b. 160
   c. 180
   d. 200

7. The development of diabetes mellitus can be multifactorial. Predisposing factors that may play a role include
   a. Chronic pancreatitis
   b. Obesity
   c. Hyperadrenocorticism
   d. All of the above

8. Proper insulin handling is important; therefore, all insulin preparations should be gently mixed before administration.
   a. True
   b. False

9. Glucose is stored in the liver as
   a. Globulin
   b. Glycogen
   c. Glucagon
   d. Gastrin

10. Glucose curves are performed once every ________ days, until an adequate curve is achieved.
    a. 2–5
    b. 4–7
    c. 7–10
    d. 12–15

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