Diabetes Mellitus

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Introduction and Overview

Diabetes mellitus is a complex endocrine metabolic disorder that results in abnormally high blood glucose ("blood sugar") concentrations, a condition called hyperglycemia, and glucose in the urine (glycosuria). The disease was first named 'diabetes' almost 600 years ago in Greece, with the term referring to the excessive urination associated with the disease. In the 1600's the term 'mellitus', which means 'like honey' in Greek, was added to reflect the sweet smell and taste of the patient's urine. The primary cause of diabetes mellitus is a lack of activity of the hormone insulin, and two main forms of the disease are recognized in people and pets.

Type I diabetes is characterized by an inability of the beta cells of the pancreas to produce insulin. As a result, circulating concentrations of insulin are far too low to exert its effects on cells in the body. In people, Type I diabetes mellitus is also known as 'juvenile onset diabetes' as it tends to occur in young people. Type II diabetes is caused by an inability of insulin to exert its effect at the cellular level. Because the problem is not the lack of insulin, this form of the disease is called 'insulin resistant diabetes' to reflect the fact that the cells fail to respond to the insulin that is present. In people, this is the most common form of the disease. Although it previously was known as 'adult onset diabetes,' it is becoming more prevalent in children and is strongly associated with childhood obesity. The underlying causes of most cases diabetes mellitus are not known. However, some known factors can trigger the onset of diabetes including exposure to some drugs, abdominal tumors, pancreatitis, and surgical procedures. According to a 2004 survey completed by the makers of Vetsulin (an FDA-approved veterinary product for the treatment of diabetes mellitus in both dogs and cats), approximately 1 in every 500 dogs suffers from diabetes mellitus. Survey results also showed that of the more than 200 veterinarians polled, 70% had between one and 10 diabetic canine patients, and 26% had 11 or more diabetic canine patients. Because West Highland White Terriers are one of the breeds predisposed to develop diabetes mellitus, it is important for owners to understand the signs and symptoms of the disease, the disease process, and treatments available.

The Pancreas

The pancreas, an elongated organ located near the beginning of the small intestine (i.e., adjacent to the duodenum), secretes substances into the intestine that are critical to normal digestion of food and into the bloodstream that are important in regulating blood glucose concentrations. The latter function of the pancreas is referred to as its endocrine role in the body. Consequently, we will focus our attention on the endocrine function of the pancreas.

The parts of the pancreas that have endocrine functions include clusters of cells called the "Islets of Langerhans" which can easily be recognized in microscopic examinations of the organ **(Figure 5.6).** The islets are made up of three major cell types (alpha, beta, and delta cells), each of which secretes specific

Common Clinical Findings
Excessive Thirst
Frequent Urination
Weakness and Weight Loss
High Fasting Blood Glucose
Glucose in the Urine

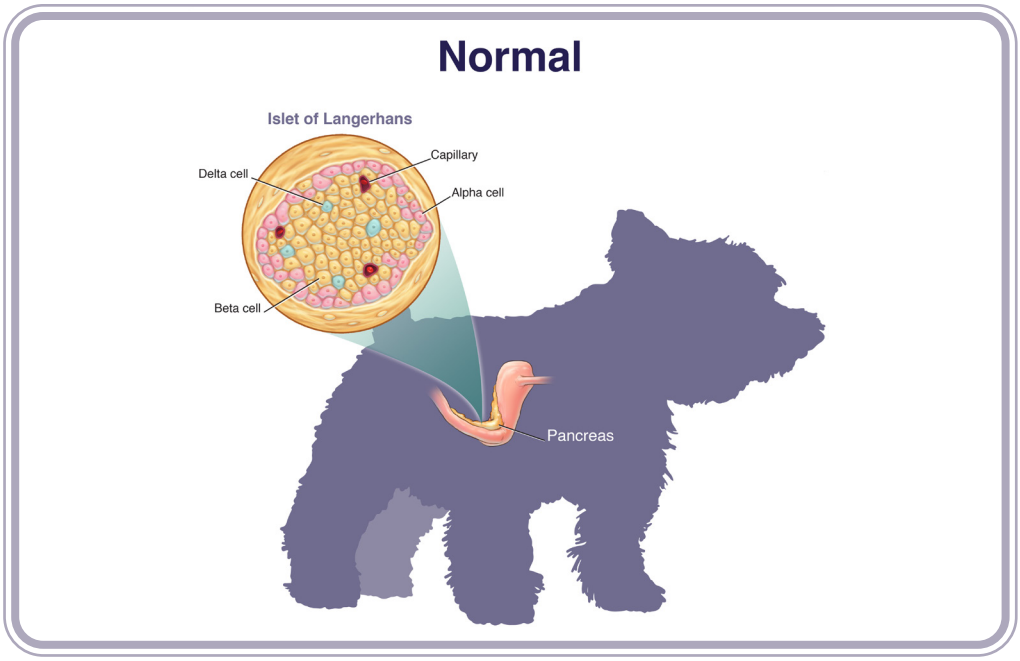

Figure 5.6 - In the normal dog, the pancreas contains specialized clusters of cells called Islets of Langerhans. These consist of alpha, delta and beta cells; beta cells are responsible for the synthesis of insulin.

hormones. The alpha cells secrete glucagon (which increases blood glucose levels), the beta cells secrete insulin (which lowers blood glucose levels), and the delta cells secrete somatostatin (which regulates secretion of other hormones).

Physiologic Role of Insulin

As you might have guessed, insulin and glucagon have opposing actions. To more easily understand these effects, let's consider what happens after a large meal, particularly one that is rich in carbohydrates. When a meal such as this is eaten, digestion of the food in the small interest releases glucose molecules. These glucose molecules are absorbed by the cells that line the intestine, after which they enter the blood stream. When the concentration of glucose in the blood increases, the beta cells in the pancreas secrete insulin into the blood. The insulin then interacts with specific receptor proteins on the surface of most cells in the body, like muscle and fat cells. As a result of insulin binding, these cells insert special glucose transporter ('channel') proteins in their membranes. These transporter proteins then allow glucose to enter the cells where it is metabolized to generate much of the energy the cell needs to function or, as occurs in muscle cells, to be stored in long chains as glycogen. Extra glucose molecules also can enter the cells in the liver where they can be stored as glycogen. The overall effect of the uptake, metabolism and storage of glucose from the blood is a decrease in the blood glucose concentration.

As the concentration of glucose in the blood decreases, the alpha cells in the pancreas respond by secreting glucagon. Glucagon exerts its effect on the liver to release the glucose that has been stored as glycogen or to synthesize new glucose molecules. As these glucose molecules enter the blood stream and increase the glucose concentration, the beta cells respond by increasing insulin secretion. In the normal person or animal, this interplay between insulin and glucagon result in blood glucose concentrations remaining within a fairly narrow normal range of values, typically between 70 and 110 mg/dl. As you know, the function of the kidneys is to remove wastes from the blood. To do this, the kidney acts as a filter. However, there are components of the blood that the body does not want to lose, and one of these is glucose. As a result, all of the glucose filtered from the blood is reabsorbed by cells in the kidney. When blood glucose concentrations are less than 180 mg/dl, essentially none of the glucose makes it into the urine. This is an extremely efficient way of maintaining blood glucose concentrations within the normal range.

What happens in diabetes mellitus?

In diabetes mellitus, there is either insufficient synthesis of insulin by the beta cells in the pancreas (Type I diabetes) or the insulin that is secreted cannot trigger the cells in the body to insert the transporter proteins into their membranes (Type II diabetes). In both cases, glucose molecules are unable to enter the cells to be metabolized or stored as glycogen. To compensate for the resulting low intracellular concentration of

> Type I diabetes mellitus is the most common form of the disease in dogs, and is caused by destruction of the pancreatic beta cells.

glucose, a metabolic process called glycogenolysis begins. As its name would suggest, glycogenolysis lyses the glycogen molecules, thereby making even more glucose available. The glucose molecules accumulate in the circulation, resulting in blood concentrations much higher than 180 mg/dl (>400 mg/dl). This high blood level of glucose exceeds the amount the kidney can reabsorb, and glucose enters the urine. Consequently, in the absence of insulin, a paradox exists: glucose concentrations are high in the blood, low inside the cells, and lost into the urine.

When the glycogen stores are utilized, the body looks to other potential sources of energy. One of these involves lipolysis (lysis of fats). While this approach is initially beneficial, fat metabolism can result in the generation of substances called ketones, a decrease in the pH of the animal's blood (i.e., ketoacidosis), and eventually death. Diabetes mellitus, if unmanaged, can be life-threatening. It is another paradox of this disease – nutrients are available to cells in the circulation, but without insulin, the cells are starving. Starvation at the cellular level may be associated with increased appetite and eating (polyphagia). Consequently, dogs with long-term, poorly-controlled diabetes may actually waste away as body stores of calories are used up.

Type I Diabetes Mellitus

Type I diabetes mellitus is the most common form of the disease in dogs, and is caused by destruction of the pancreatic beta cells as the result of a combination of autoimmunity, genetics and environmental factors (**Figure 5.7**). Based on the evidence that dogs and people develop immune responses to pancreatic islet proteins and cells involved in immune reactions may destroy islet cells, many people have concluded that autoimmunity plays a key role in the development of diabetes. There also is evidence that pedigree dog breeds, including Australian Terriers, Samoyeds, Miniature Schnauzers, Westies and Cairn Terriers, have a higher risk of developing diabetes mellitus, whereas others (e.g., Boxer) appear to be far less likely to develop the disease. Consequently, genetic factors may be important in the development of the condition, much like the situation in human. As dogs and humans with this form of the disease require insulin injections to control their blood glucose concentrations, type I diabetes mellitus has been called "insulin-dependent diabetes."

Although any dog can develop Type I diabetes mellitus, the disease typically affects dogs that are middle aged (6-9 years old) and intact bitches. The clinical signs commonly associated with Type I diabetes include polydypsia (increased

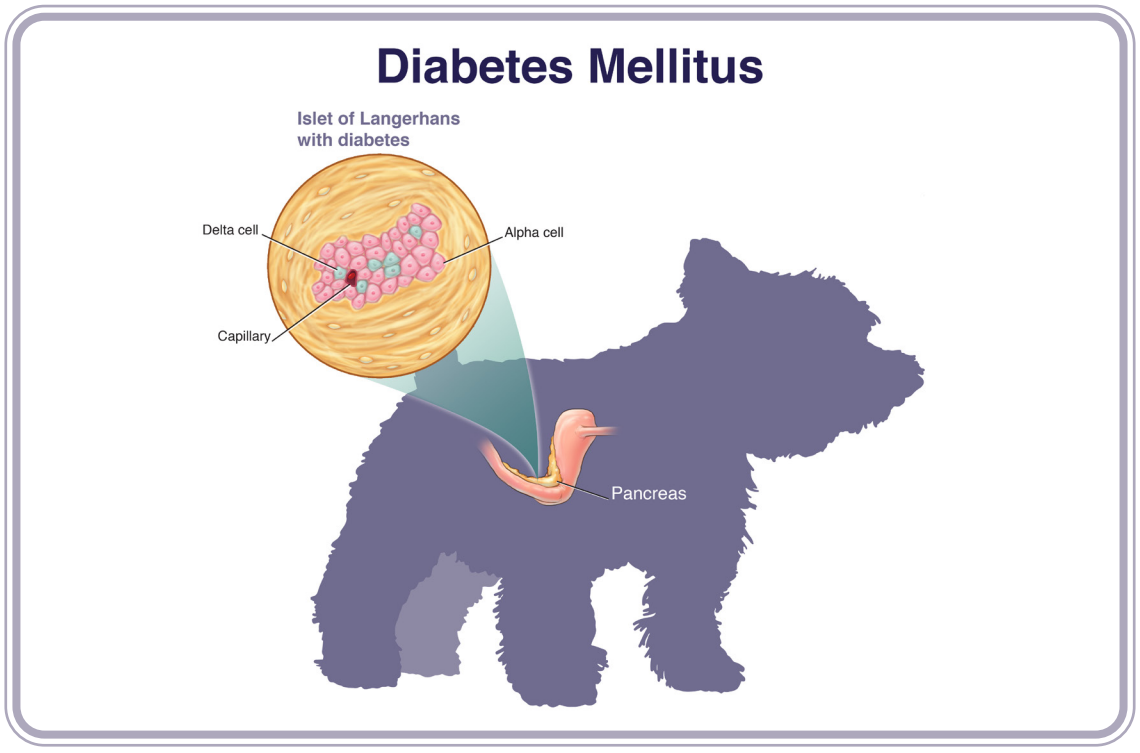

Figure 5.7 - In dogs with Type 1 diabetes, damage to the pancreas results in islets that are essentially devoid of functioning beta cells.

thirst), polyuria (frequent urination), polyphagia (increased hunger), weakness, weight loss, increased susceptibility to infections (such as skin infections or urinary tract infections), depression and potentially loss of vision due to cataract formation.

Diagnosis of Type I Diabetes Mellitus

Although a veterinarian may presume that a dog with the clinical signs mentioned above (excess thirst, urination, appetite and weight loss) may have Type I diabetes mellitus, blood and urine samples will need to be tested to make the diagnosis. It is critical that the correct diagnosis is made, as there are other diseases that could cause these same clinical signs. The laboratory tests that typically are performed are to detect hyperglycemia (high fasting blood glucose concentration) and glucosuria (glucose in the urine). Because blood glucose concentrations can increase substantially after a meal, the blood sample will need to be taken several hours after the dog's latest meal. There also may be other abnormalities identified in the blood, including some associated with high concentrations of ketones in the blood. Examples of these include high levels of cholesterol and serum enzymes leaking from cells in the liver. If the blood concentration of glucose is increased, the veterinarian will need to consider other possible conditions, most of which can be eliminated based on the dog's history and any current treatments. These include a recent history of administration of glucocorticoids or IV glucose, accidental exposure to ethylene glycol (anti-freeze), inflammation of the pancreas, or a pancreatic tumor that secretes glucagon.

Treatment of Type I Diabetes Mellitus

Treatment of dogs with Type I diabetes mellitus includes a few important goals, namely providing a sufficient amount of insulin (by injection) to adequately control blood glucose concentrations, preventing the development of glucosuria, minimizing the clinical signs of diabetes, and reducing the likelihood that long-term complications will develop. This requires tweaking the amount of insulin needed until the optimal results are obtained, a process that typically takes several weeks. During which time, the veterinarian will repeatedly monitor blood glucose concentrations, test the urine for the presence of glucose, and evaluate the dog's clinical signs. The goals will be to reduce the incidence of polydipsia, polyuria and ketonuria, maintain blood glucose concentrations between 60 and 160 mg/dl, and prevent the development of low blood glucose (hypoglycemia; <50 mg/dl).

Type II Diabetes Mellitus

This form of diabetes mellitus is much less common in dogs and will only be briefly discussed. In people, Type II diabetes is far more common, and is known as adult-onset or noninsulin-dependent diabetes. Rather than there being a lack of insulin, this form of diabetes occurs when the beta cells in the pancreas produce less than optimal amounts of insulin, these cells are slow in secreting it or the dog's tissues are resistant to its effects. Type II diabetes tends to occur in older obese dogs. While the exact cause is unknown, excess weight and inactivity appear to be important factors. While people with Type II diabetes can be treated with drugs that stimulate the remaining beta cells to increase their production of insulin, this therapy does not appear to work as well in dogs. As with Type I diabetes, if left undiagnosed, the results of Type II diabetes can be fatal. There is no current cure, although it can be prevented and managed by eating healthy, exercising, and maintaining a healthy weight.

Complications of Diabetes Mellitus

The two most commonly encountered complications of untreated or poorly treated diabetes in dogs involve the eye. One of these is the development of cataracts, a condition characterized by a cloudy appearance of the normally clear lens within the eye. Cataracts typically develop fairly rapidly as the excess glucose in the aqueous humor (fluid adjacent to the lens) diffuses into the lens where it is metabolized to two other sugar molecules that are then trapped within the lens. Because these two sugar molecules cannot leave the lens, they draw water from the aqueous humor into the lens, causing it to swell and become cloudy. In healthy dogs, the concentration of glucose in the aqueous humor never reaches the high concentrations that trigger this complication. This is yet another reason to administer insulin to dogs with Type I diabetes, as keeping glucose concentrations within normal limits will minimize the likelihood that cataracts will form.

The other complication of diabetes mellitus that affects the eye is glaucoma, a condition in which pressure within the eye increases. If the pressure becomes excessive, it will cause damage to the optic nerve that connects the retina to the area of the brain that is allocated to vision. Glaucoma can have many causes but it usually is caused by a narrowing or obstruction of an angle at the front of the eye beneath the cornea through which the aqueous humor normally flows out of the eye. Glaucoma can lead to intense ocular pain, decreased vision, and, in many cases, blindness.

Summary and Important Points

Diabetes mellitus is a relatively common metabolic disease in dogs, including West Highland White Terriers, but that fortunately is treatable with good success. The causes are unknown but include pancreatic disease, genetics and possible environmental factors. Common signs are increased thirst (polydipsia), increased urination (polyuria), and appetite (polyphagia). Blood and urine tests are used to identify the high concentrations of glucose in the blood and the presence of glucose in the urine. Treatment usually involves giving daily injections of insulin that are sufficient to meet daily metabolic needs and monitoring blood glucose concentrations. If left untreated, diabetes mellitus can cause ketoacidosis, coma, glaucoma, coma, and even death. Properly treated dogs can live relatively normal lives.

Current Research About Diabetes Mellitus

O'Kell AL, Davison LJ. Etiology and Pathophysiology of Diabetes Mellitus in Dogs. Vet Clin North Am Small Anim Pract 2023 May;53(3):493-510.

Canine diabetes results from a wide spectrum of clinical pathophysiological processes that cause a similar set of clinical signs. Various causes of insulin deficiency and beta cell loss, insulin resistance, or both characterize the disease, with genetics and environment playing a role. Understanding the genetic and molecular causes of beta cell loss will provide future opportunities for precision medicine, both from a therapeutic and preventative perspective. This review presents current knowledge of the etiology and pathophysiology of canine diabetes, including the importance of disease classification. Examples of potential targets for future precision medicine-based approaches to therapy are discussed.

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The mechanisms implicated in the development of diabetic kidney disease in people are present in dogs and cats and, in theory, could lead to renal complications in companion animals with long-standing diabetes mellitus. However, these renal complications develop during a long period, and there is little to no clinical evidence that they could lead to chronic kidney disease in companion animals.

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Understanding the effects of diabetes and hyperglycemia on hydration, acid-base status, and immune function is paramount to safely anesthetizing diabetic cats and dogs. Preoperative stabilization of glucose concentrations, hydration, and electrolyte imbalances is key to minimizing morbidity and mortality. Blood glucose monitoring perioperatively will help guide insulin and dextrose administration. Specific anesthetic considerations, and peri-anesthetic management of animals with diabetes mellitus, including anesthetic drugs and recommended insulin protocols are discussed.

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