

# The Canine Endocrine Pancreas



From The WALTHAM Course on Dog and Cat Nutrition.  
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## KEY POINTS

- **Diabetes mellitus is the most common disorder of the endocrine pancreas.**
- **It is not a single disease, but a disorder of the carbohydrate, protein, and lipid metabolism.**
- **Diabetes mellitus is characterized by an insulin deficiency, which leads to a glucagon-driven uncontrolled gluconeogenesis by the liver.**
- **This can be caused by an autoimmune-mediated destruction of the pancreatic islets resulting in true insulin deficiency, or as a result of impaired insulin secretion and peripheral insulin resistance.**
- **The diagnosis of diabetes mellitus is based on clinical findings, such as polydipsia and polyuria, weight loss, and exercise intolerance, coupled with laboratory findings, including hyperglycemia and glucosuria.**
- **The management of diabetes mellitus aims at achieving adequate glycemic control and includes the treatment of possible underlying conditions, the provision of insulin, dietary manipulations, and exercise modification.**
- **The appropriate insulin therapy needs to be established for each individual patient through individual stabilization and maintenance protocols.**
- **The dietary management includes achieving and maintaining an ideal body weight and supporting glycemic control.**
- **Diets containing complex carbohydrates, such as starch and fiber, are beneficial, as carbohydrates are released slowly, and reach the blood stream over an extended period of time. It is best to use a diet containing a blend of soluble and insoluble fiber.**
- **Additionally, the appropriate feeding regimen, such as feeding to coincide with insulin therapy, is important.**
- **Diabetic ketoacidosis is a life-threatening complication of diabetes mellitus**
- **Ketoacidosis needs to be corrected slowly by providing intravenous fluids, correcting possible electrolyte imbalances, and providing adequate insulin.**

The pancreas has both exocrine and endocrine functions. **Diabetes mellitus**, which results from an absolute or relative insulin deficiency because of impaired insulin secretion or insulin resistance, is the most common disorder associated with dysfunction of the endocrine pancreas. The prevalence of diabetes mellitus is similar in the dog and cat and has been estimated to be between 0.0005% and 1.5%. It is considered to be one of the three most common endocrine disorders of the dog (with hypothyroidism and hyperadrenocorticism), and the second most common (to hyperthyroidism) of the cat.

## ANATOMY

In both dogs and cats, the pancreas is a V-shaped organ with the angle pointing forwards and lying caudomedial to the pylorus. The endocrine pancreas is composed of the islets of Langerhans, which are dispersed as small clusters of cells throughout the exocrine tissue.

Each islet is a highly vascularized cluster of several types of cells. Four cell types are common to all species and include:

- $\beta$  cells which secrete insulin
- $\alpha$  cells which secrete glucagon
- $\delta$  cells which secrete somatostatin
- F cells which secrete pancreatic polypeptide

## FUNCTION

The major function of the endocrine pancreas is related to insulin and glucagon production. The actions of these hormones are counter-regulatory, but together they ensure the efficient storage, utilization, and metabolism of ingested nutrients.

Insulin is a protein consisting of 51 amino acids contained within two peptide chains linked by disulfide bridges, an A chain with 21 amino acids and a B chain with 30 amino acids. It is formed by the cleavage of a connecting peptide (C peptide) from a precursor molecule (proinsulin) within the secretory granules of the  $\beta$  cell. Insulin and C peptide are secreted in equimolar amounts. C peptide has not yet been shown to have any significant bioactivity.

Insulin reaches the liver via the portal circulation where more than half is retained. It then circulates unbound to plasma proteins and exerts its effect on target cells after binding to specific plasma membrane receptors. The major action of insulin is in the promotion of storage of nutrients. Insulin promotes glucose uptake, and lipid and protein anabolism and storage while inhibiting glycogenolysis, gluconeogenesis, lipolysis, ketogenesis, and proteolysis.

Glucagon is a single chain peptide consisting of 29 amino acids. Its secretion and actions are intricately linked with those of insulin. Glucose is the most potent stimulator of insulin release, although other sugars, such as mannose and fructose, and amino acids such as leucine, also play a role. Various gastrointestinal hormones such as gastrointestinal peptide, cholecystokinin, secretin, and gastrin, released upon food intake serve to potentiate insulin secretion. Insulin secretion is also directly stimulated by small changes in the secretion of glucagon.

Catecholamines and somatostatin inhibit insulin release, although this is of minor significance. Glucagon secretion is stimulated by many amino acids, catecholamines, gastrointestinal hormones, and glucocorticoids and is inhibited by glucose, insulin, and somatostatin. Glucagon promotes glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis while inhibiting glycogen synthesis.

During starvation, glucagon activity predominates, releasing stored fuels and ensuring an adequate circulating glucose concentration for optimal neurologic function, as this is largely dependent on passive diffusion of glucose. Insulin activity predominates in the fed state, although a diet high in protein will stimulate glucagon secretion to prevent hypoglycemia resulting from protein stimulated post-prandial insulin secretion.

## DIABETES MELLITUS

Diabetes mellitus is not a single disease, but rather a heterogeneous disorder of carbohydrate, protein, and lipid metabolism with multiple possible etiologies. In all cases, there is an absolute or relative insulin deficiency combined with an absolute or relative excess of glucagon, thereby compromising the body's ability to regulate nutrient metabolism.

In affected animals, insulin deficiency allows glucagon-driven gluconeogenesis by the liver to proceed uncontrolled. This increase in glucose production is exacerbated by reduced insulin-dependent uptake of glucose from the circulation resulting in hyperglycemia and the clinical state of uncomplicated diabetes mellitus.

As the supply of glucose for fuel is compromised, ketones are generated in the liver from mobilized lipid stores as alternative energy substrates, a pathway enhanced by the altered insulin:glucagon ratio. The principal ketones are acetoacetic acid, acetone, and  $\beta$ -hydroxybutyrate. While of short-term benefit for energy supply, insulin deficiency decreases utilization of ketone bodies by peripheral cells. As ketones continue to be produced and then accumulate in the blood, the body's buffering system becomes overwhelmed, culminating in the clinical state of complicated diabetes mellitus or **diabetic ketoacidosis**.

## Classification

In humans, there are two major groups of diabetic patients – type I and type II.

Type I disease usually develops in young lean individuals as a result of autoimmune destruction of the pancreatic islets and true insulin deficiency. These patients invariably require exogenous insulin therapy to prevent ketoacidosis and death.

Type II disease develops in older patients as a result of impaired insulin secretion and peripheral insulin resistance. Notable risk factors are advancing age, reduced activity, and obesity. The characteristic histopathologic finding is marked amyloid deposition in the pancreas. These patients rarely develop ketoacidosis and can often be controlled by oral hypoglycemic agents and **dietary management** alone.

There is a tendency to use the terms insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) synonymously with type I and type II disease, respectively. However, etiologic states may not necessarily run parallel with pathophysiologic states, for example, some type II diabetics eventually become insulin dependent.

Another type of diabetes mellitus exists in humans, called secondary or type II disease. This arises from another primary disease process producing destruction of  $\beta$  cells or insulin resistance, such as generalized pancreatic disease or injury, effects of antagonistic hormones, or prolonged diabetogenic drug administration.

In canine diabetes mellitus, insulin dependency is common. However, type I disease or autoimmune destruction of the pancreatic islets is infrequently recognized and many other possible etiologies exist; broadly classified as a failure of insulin production or reduced peripheral sensitivity to insulin. In the latter case, increased insulin production by the pancreas will initially compensate for altered tissue sensitivity. However, eventually  $\beta$  cell exhaustion results or insulin production may be inhibited by glucose leading to a state of at least temporary

insulin dependency. Classification of canine diabetes mellitus may therefore be better achieved by reference to the principal underlying etiology if it is known or can be surmised.

### *Factors Capable of Causing or Contributing to Diabetes Mellitus in Dogs*

<b>Decreased Insulin Production</b>	<b>Enhanced Insulin Resistance</b>
<b>Autoimmune islet destruction</b>	<b>Obesity</b>
<b>Islet cell hypoplasia</b>	<b>Hormonal antagonism</b>
<b>Pancreatitis</b>	<b>Glucagon (uremia, stress, glucagonoma)</b>
<b>Pancreatic neoplasia</b>	<b>Glucocorticoids (hyperadrenocorticism, exogenous, stress)</b>
<b>Pancreatic injury</b>	<b>Catecholamines (pheochromocytoma, stress)</b>
<b>Drug/chemical toxicity</b>	<b>Growth hormone (progesterone/progestogen induced)</b>
<b>Senile islet degeneration</b>	

## **Glucose Toxicity**

Glucose toxicity describes the often reversible phenomenon of inhibition of insulin secretion by persistent marked hyperglycemia. Long-term hyperglycemia causes down-regulation of the glucose transporters on  $\beta$  cell membranes, resulting in reduced insulin secretion. It is well documented in cats, where it can lead to an erroneous diagnosis of insulin deficiency in type II disease. In dogs, it provides an alternative explanation to  $\beta$  cell exhaustion as a cause of insulin dependency resulting primarily from peripheral insulin resistance.

## **Historical and Clinical Signs**

Diabetes mellitus is typically a disorder of middle-aged and older dogs. Females, particularly entire females, are at increased risk of developing the condition and breed predispositions are variable.

Most diabetic dogs are alert and reasonably bright when initially presented and exhibit some, or all, of the following features:

- **Polyuria and polydipsia**
- **Polyphagia**
- **Weight loss**
- **Exercise intolerance/decreased activity**
- **Cystitis**
- **Cataracts**
- **Hepatomegaly**

The classic features of polyuria and polydipsia are the result of osmotic diuresis. Once the blood glucose concentration exceeds 10 to 12 mmol/l, glucose spills over into the urine resulting in polyuria and a compensatory polydipsia.

Polyphagia occurs because the hypothalamic satiety center is dependent on insulin-mediated glucose transport to assess the body's need for food. Weight loss occurs as a result of the mobilization of the body's lipid and protein sources for gluconeogenesis in the liver and the loss of glucose as an energy source. The influx of lipid eventually results in hepatic lipidosis detected physically as hepatomegaly.

Diabetic dogs are at increased risk of developing cystitis because glucosuria provides a nutrient-rich environment which, when coupled with the immunosuppressive effects of diabetes mellitus and possible urinary retention, favors bacterial proliferation.

Cataracts result from osmotic disruption of the lens due to an accumulation of sorbitol, which diffuses out of the lens slowly. Metabolism of glucose to sorbitol only occurs when intralenticular glucose concentrations are excessive.

If untreated, diabetes mellitus can progress to life-threatening **ketoacidosis**.

### *Laboratory Findings*

#### *Hematology*

- Mild nonregenerative anemia
- Stress leukogram

#### *Biochemistry*

- Hyperglycemia
- Increased liver enzymes (alkaline phosphatase [LKP], alanine aminotransferase [ALT])
- Hypercholesterolemia
- Hypertriglyceridemia
- Increased fructosamine
- Increased glycosylated hemoglobin

#### *Urinalysis*

- Glucosuria
- Evidence of urinary tract infection (alkaline pH, protein, blood, bacteria)
- Positive urine culture if cystitis present

## Diagnosis

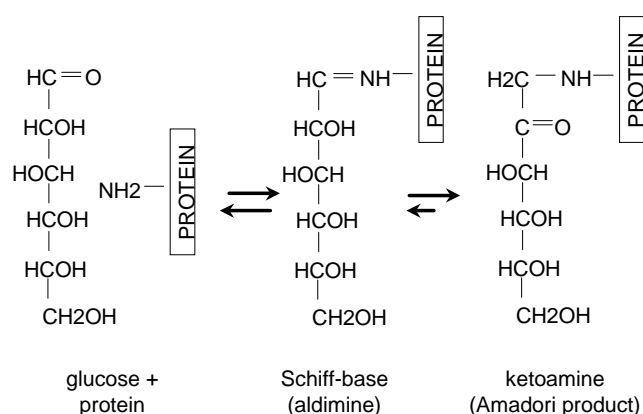
A diagnosis of diabetes mellitus is based on the presenting clinical features coupled with demonstration of hyperglycemia and glucosuria. Both analyses are required simultaneously as mild hyperglycemia can occur in unrelated conditions (pancreatitis, glucocorticoid excess, growth hormone excess, pheochromocytoma, hepatic disease) and glucosuria can occur without hyperglycemia (primary renal glycosuria, Fanconi syndrome).

Demonstration of elevated circulating concentrations of **glycated protein** serves to confirm a diagnosis of diabetes mellitus and provides supportive evidence of its duration.

## Glycated Proteins

Assessment of circulating glycated protein concentrations is widely used in the diagnosis of diabetes mellitus and as a means of **monitoring therapeutic efficacy**. Commonly assayed glycated proteins include:

- **Glycosylated Hemoglobin** - the product of glucose chemically binding to hemoglobin in circulating red blood cells. Its concentration is dependent on the prevailing blood glucose concentrations over the lifespan of the erythrocyte, considered to be approximately 100 days in dogs.
- **Fructosamine** - the product of an almost irreversible nonenzymatic reaction between glucose and plasma proteins, mainly albumin. Its concentrations are dependent on the prevailing blood glucose concentrations over the half-life of albumin, considered to be 7 to 21 days in dogs.



*Fructosamine is the product of a nonenzymatic reaction between glucose and serum proteins. The first stage in this reaction is the condensation of the free aldehyde group of a sugar with the amino group of a protein. This results in an unstable Schiff-base compound (aldimine) that can freely dissociate back into sugar and protein. Alternatively, such compounds can undergo molecular transformation by Amadori rearrangement into much more stable ketoamines that can be easily measured.*

## **Management**

The management of diabetes mellitus involves considerable input on the part of the veterinary surgeon and owner. Despite this, the treatment is usually successful in achieving adequate glycemic control and the regimen can become a simple daily routine. Management involves all of the following:

- **Identification and treatment of any underlying/precipitating cause**
- **Provision of insulin**
- **Dietary management**
- **Exercise modification**
- **Preventive therapy for hypoglycemia**
- **Problem diabetics**

### ***Identification and Treatment of Any Underlying/Precipitating Cause***

Diabetes mellitus may be caused by or exacerbated by many different factors. In many cases, little can be done to redress the underlying cause (e.g., islet cell autoimmunity) and treatment involves insulin administration and exercise and dietary modification. In other cases, a definite predisposing factor can be identified and addressed, such as:

- Pancreatitis
- Obesity
- Glucocorticoid excess
- Growth hormone excess (progesterone/progestogen excess)
- Catecholamine excess
- Glucagon excess

Successfully treating these conditions rarely results in a permanent cure of the diabetic state, but frequently improves glycemic control and decreases exogenous insulin requirements. The best and most common example of a “cured” diabetic dog is the bitch that undergoes ovariohysterectomy before  $\beta$  cell exhaustion takes place.

### ***Provision of Insulin***

All diabetic dogs require daily insulin therapy by subcutaneous injection, at least initially, to control the hyperglycemia and associated clinical signs. Insulin can be broadly classified as:

- Short-acting (neutral, soluble, regular)
- Intermediate-acting (neutral protamine Hagedorn [NPH], Lente, biphasic)
- Long-acting (protamine zinc insulin [PZI], Ultralente)

It can also be classified as to its origin as:

- Bovine
- Porcine
- Recombinant human

Bovine or porcine insulin is used most frequently. Canine insulin is most similar to porcine insulin, but problems with antibody production rarely occur with bovine insulin.

Because of its rapid onset and short duration of action, neutral insulin is used in the treatment of diabetic ketoacidosis. Lente insulin is most commonly used in the chronic daily management of the condition and is presumed to have duration of activity of up to 24 hours. The treatment objective is to stabilize the patient on an appropriate dose of insulin, and thereafter to maintain glycemic control using an appropriate and fixed dose.

PZI insulin is a longer-acting preparation and may be used when the duration of Lente insulin is suboptimal. Compared to Lente insulin it is poorly absorbed subcutaneously, and higher doses may need to be used to achieve similar glycemic control.

### **Stabilization Regimes**

There are many published protocols for stabilization of diabetes mellitus. The first step is to reduce the number of variables that can affect the response to insulin. In effect, this involves selection of an appropriate diet, divided and timed, to coincide with insulin therapy and deciding on a regular exercise plan.

Appropriate insulin is chosen and the injection time is selected to fit in with the owner's lifestyle. Initially, a low dose of insulin is administered and daily dosage adjustments are made based on urinary glucose output or blood glucose measurements.

### ***Stabilization Protocol Using Urinalysis***

- Once-daily injection of intermediate-acting insulin
- Two evenly divided meals fed 6 to 8 hours apart (first at time of injection)
- Starting dose of insulin of 0.5 to 1.0 IU/kg
- Pre-injection urine glucose measurement using reagent strips
- Adjust dose by approximately 10% or 0.1 IU/kg

Negative urine glucose -	Reduce dose
0.1% to 1% glucosuria -	Leave dose
≥ 2% glucosuria -	Increase dose

- Record insulin doses and urine glucose results
- Eventually insulin doses even out and swing around a mean dose (usually 1 to 1.5 IU/kg), which can be selected and adhered to. This usually takes 2 to 3 weeks. Further adjustments can be made based on assessments during the maintenance period.

The main problem using this protocol is the possibility of inducing the **Somogyi overswing**. This can be avoided by measuring urine glucose output three times a day, however, this may be difficult for owners to implement. In addition, the protocol is dependent on maintenance of mild hyperglycemia and glucosuria, and its attendant clinical signs. This can be avoided by frequent monitoring of blood glucose concentrations weekly, at least initially.

#### *Insulin Dose Adjustments Using Three Times Daily Urine Glucose Measurements*

7 hours Post Injection	13 to 14 hours Post Injection	Just Before Insulin	Dose Adjustment
Negative	Negative	Trace	None
Positive	Positive	Positive	Increase by 10%
Negative	Negative	Negative	Decrease by 10%
*Negative	Positive	Positive	Decrease by 20%
Negative	Negative	Positive	None
Negative	Positive	Trace	None

\* Indicates Somogyi overswing.

#### *Stabilization Protocol Using Blood Glucose Measurement*

- Once-daily injection of intermediate-acting insulin
- Two evenly divided meals fed 6 to 8 hours apart (first at time of injection)
- Starting dose of insulin of 0.5 to 1.0 IU/kg
- Measure nadir (pre second feed) blood glucose and adjust dose
 

< 3.5	mmol/l -	Reduce dose
3.5 – 7	mmol/l -	Leave dose
7.5 – 15	mmol/l -	Small increase in dose (10%)
> 15	mmol/l -	Large increase in dose (20%)
- Record insulin doses and blood glucose results

- Select a mean dose that keeps nadir blood glucose between 3.5 and 7.5 mmol/l. Usually a dose is selected that has been the same for 3 to 4 days (usually takes 10 to 14 days with a final dose of between 1 and 1.5 IU/kg). Further adjustments can be made based on assessments during the maintenance period.

Normally diabetic dogs are hospitalized for this stabilization protocol. However, provided the owner can return the dog to the veterinary clinic for blood glucose determinations at the appropriate time of day, this is not strictly necessary. Obviously, a means of accurately quantifying blood glucose concentrations in-house is a prerequisite.

### **Maintenance and Monitoring Protocols**

During the maintenance period, the insulin, diet, and exercise regimens are not usually dramatically altered unless a problem occurs. Glycemic control is initially assessed and fine-tuned at least weekly, and after every adjustment, then monthly, then every 3 months or as indicated clinically. Assessment of glycemic control is based on:

- **Owner Report**

Given time, most owners of diabetic animals will be able to accurately report on the level of glycemic control achieved in their pet by monitoring clinical signs such as attitude, water intake, appetite, and frequency of hypoglycemic episodes.

- **Physical Examination**

A full physical examination, including weight and diabetic cataract check, will assist in determining adequacy of glycemic and dietary control and in alerting the clinician to any concurrent problems that may have developed.

- **Nadir Blood Glucose**

Assessment of the animal can be timed to coincide with the expected nadir blood glucose concentration. For once-daily Lente insulin injections, this typically occurs 6 to 8 hours after insulin injection, before the second meal of the day.

- **Glycated Proteins**

Assessment of circulating fructosamine or glycosylated hemoglobin concentration provides evidence of the level of glycemic control in the previous 1 to 3 weeks or 3 months, respectively.

- **Blood Glucose Curve**

Serial blood glucose determinations over 24 hours were previously recommended in order to assess the duration of insulin activity, its efficacy, and the adequacy of the meal times and

proportions. With the advent of glycated protein measurements, this has been largely superseded, but is still an invaluable tool in the investigation of **problem diabetics**.

### *Using Fructosamine Measurements to Assess Diabetic Stability*

<b>Fructosamine (<math>\mu\text{mol/l}</math>)</b>	<b>Dog</b>	<b>Cat</b>
<i>Fair control</i>	< 450	< 550
<i>Poor control</i>	> 450	> 550

*\* These ranges are guidelines only. Each laboratory will supply its own range.*

## ***Dietary Management***

Dietary management is the cornerstone in the treatment of diabetes mellitus. The objectives of dietary management of diabetic dogs are to provide adequate nutrients for:

- Achieving and maintaining ideal body weight and condition
- Optimization of conditions for achieving good glycemic control
- Dietary management of concurrent diseases or complications of diabetes mellitus

### **Achieving and Maintaining Ideal Body Weight and Condition**

A well-balanced diet should be fed in amounts sufficient to meet the caloric needs of the individual as follows:

- **Dogs of Ideal Body Weight and Condition**

Generally the daily caloric needs of a well-controlled diabetic dog are similar to those of a normal healthy dog. Initially, daily caloric requirements are calculated as for maintenance, but further adjustments to maintain steady body weight and condition may be required because of individual differences in caloric needs and degree of glycemic control achieved with exogenous insulin. Excess calories should be avoided because of resultant weight gain and potential exacerbation of the diabetic state. In addition, although obesity is most commonly associated with difficulties in diabetic management, underfeeding and malnutrition also have detrimental effects on glucose metabolism. Eventual caloric intake may therefore vary from 80% to 150% of estimated intake for maintenance of ideal body weight and condition.

- **Obese Dogs**

Obesity is known to enhance down-regulation of insulin receptors, to decrease insulin receptor binding affinity, and to cause post-receptor defects in glucose metabolism, and is therefore a

potential cause and contributor to diabetes mellitus. Weight loss is associated with improved glycemic control and decreased exogenous insulin requirements. Weight loss should be gradual and follow recommended guidelines. Maintenance energy requirements should be substituted once the animal achieves optimal body weight and condition.

- **Underweight Dogs**

If the dog is underweight, the diet should be fed at a maintenance level based on the estimated ideal body weight and condition. Short-term feeding of an energy dense ration may hasten weight gain in severely affected individuals. As with correction of obesity, the underweight dog should be monitored regularly, and maintenance rations substituted, once ideal body weight and condition are met.

### **Optimization of Conditions for Achieving Good Glycemic Control**

Optimal conditions for achieving good glycemic control include:

- **Consistent Dietary Intake**

The diet should be consistent in nutrient and energy composition and volume from day to day.

- **Coordinated Schedule**

A meal schedule that is coordinated with the physiologic effects of the administered insulin is necessary. Recommendations vary with the type of insulin used. The most commonly used protocol is to administer Lente insulin once a day. The food is divided into two equal portions and fed at the time of the insulin injection and again 6 to 8 hours later. For other insulin regimens, a serial blood glucose curve will assist in determining optimal feeding proportions and intervals.

- **Nutrient Manipulation**

Traditionally, low carbohydrate and high fat diets were recommended for human diabetic patients, based on the premise that since diabetic patients cannot regulate blood sugar concentrations adequately, dietary sugar should be restricted. Fat was considered a useful alternative energy nutrient but unfortunately in the long-term, can manifest in clinical complications such as ketoacidosis, pancreatitis, and hepatic lipidosis. Current recommendations are very different and involve manipulation of the proportion and physical form of the energy-giving nutrients.

### ***Carbohydrates***

Diabetic patients experience considerable difficulty in regulating blood sugar concentrations adequately, and wide fluctuations may occur even when exogenous insulin is administered.

When using a diet low in simple, and high in complex carbohydrates, the gut can act as a reservoir, slowly releasing glucose into the blood over an extended period of time, and in this way can compliment the action of insulin.

- **Simple Sugars**

Simple sugars such as glucose, sucrose, and lactose are rapidly absorbed from the gastrointestinal tract and can give rise to a sudden and marked elevation in blood glucose concentration that is difficult to coincide with insulin activity. It is for this reason that diets high in simple sugars are avoided in diabetic management.

- **Complex Carbohydrates**

Complex carbohydrates are divided into starches and dietary fiber. By comparison to simple sugars, starches are digested relatively slowly and result in a more gradual release of glucose into the circulation over several hours, complimenting the activity of exogenous insulin. The addition of fiber to the diet acts synergistically with starch. Dietary fiber slows down the rate of digestion in the lumen of the small intestine, thereby prolonging the rate of post-prandial nutrient uptake and decreasing the post-prandial blood glucose concentration. Dietary fiber is also beneficial in decreasing serum cholesterol and triglyceride concentrations, and increasing insulin sensitivity. Soluble viscous fiber tends to be more potent, such that lower concentrations are required. However, to gain optimal effects from dietary fiber, a blend of both soluble and insoluble fiber is recommended.

It has been recommended to use a diet, in which the dietary fiber has become homogenous with the dietary matrix through processing, as this is more physiologically active than fiber-rich supplements. Some high-fiber diets for dogs have been designed for weight loss, (i.e., the energy content of the food has been reduced by adding mainly insoluble fiber as a bulking agent). However, not all diabetic patients require caloric restriction, and these diets may not be appropriate for underweight or normal weight diabetics. In order to compensate for any reduced bioavailability of minerals and vitamins associated with high dietary fiber, the vitamin and mineral content of a diet should be at least 1.5 times the minimum recommendation.

Feeding an appropriate high-fiber diet can significantly reduce the degree of fluctuation of plasma glucose concentration and result in a smoother, less erratic post-prandial glycemic curve. Ultimately, this correlates with improved glycemic control and reduced exogenous insulin requirements.

### ***Fat***

In human diabetic patients, excess dietary fat is known to exacerbate hyperlipidemia and other lipid-related complications such as pancreatitis and hepatic lipidosis. High-fat diets are therefore

avoided, and the use of diets high in complex carbohydrates allows for moderate dietary fat restriction. When such diets are used, the fat content of the diet is only necessary to provide any shortfall in energy content and as a source of essential fatty acids and as a delivery route for the fat-soluble vitamins.

### ***Protein***

There is some evidence to suggest that in human type II diabetes mellitus, there is a negative correlation between protein ingestion and glycemic response because of increased insulin secretion by protein. However, increased protein consumption is not routinely recommended for human diabetics because of its associated risk with diabetic nephropathy. In dogs, diabetic nephropathy is extremely rare and therefore dietary protein restriction is not necessary. Dietary protein content should provide each individual with its recommended daily requirement.

### **Dietary Management of Concurrent Diseases or Complications of Diabetes Mellitus**

The presence of concurrent illnesses or complications such as pancreatitis, cardiac disease, renal disease, hepatic disease, and maldigestion/malabsorption have dietary priority over diabetes mellitus, as far as nutrient manipulation is concerned. However, daily caloric intake, consistency of the ration, and coordination to insulin activity remain important and should be followed as discussed.

### ***Exercise Modification***

Exercise has a lowering effect on blood glucose concentrations and should be avoided at the time of peak insulin activity. This apart, exercise should be consistent from day to day and commensurate with the dog's ability and age. Exercise in the evening may blunt overnight hyperglycemia in dogs receiving single, daily morning injections of intermediate-acting insulin.

### ***Preventive Therapy for Hypoglycemia***

Hypoglycemia becomes a potential problem in any dog undergoing insulin therapy. Fortunately it is rare, as most animals of adequate body condition are capable of instituting adequate compensatory mechanisms that respond to and correct mild hypoglycemia. Hypoglycemia can be caused by:

- Mistaken administration of an inappropriately high insulin dose
- Failure to eat proffered meals
- Inadvertent over-exercise

- Falling insulin requirements

Hypoglycemic episodes generally occur in the afternoon, when a single injection of intermediate-acting insulin is administered in the morning. Associated clinical signs are neurologic in nature because sufficient ambient glucose concentrations are necessary for normal function.

Initially the dog will appear restless and hungry. Subsequently, occasional staggering will progress to ataxia and incoordination, followed by twitching, and then lateral recumbency and seizures. Treatment involves rapid administration of glucose:

- If the dog can still eat, food can be offered; in this instance diets high in complex fiber are inappropriate and glucose rich foods such as sweets or biscuits should be offered.
- If the dog is unable to eat, glucose can be applied to the gums in the form of syrup, powder, or solution, or alternatively a 40% dextrose gel can be administered.
- If there is minimal response to the above, a 50% dextrose solution should be administered intravenously as a bolus dose of approximately 1 ml/kg followed by a 5% dextrose infusion until full recovery is achieved.

### ***Problem Diabetics***

The most common problem diabetics are those with persistent or recurrent clinical signs despite the use of apparently high doses of insulin ( $> 2$  IU/kg). These patients are commonly referred to as “insulin insensitive.” There are numerous potential causes, and investigations should follow strict guidelines to limit the number of possible differentials, such as:

- **Evaluation of Diabetic Regimen**

Evaluating the owner’s technique and assessing their ability to adhere to the strict insulin, diet, and exercise regimen may identify many of the potential problems. Problems often arise because owners are insufficiently instructed as to the correct injection technique, the proper way to store and handle insulin, or the necessity of achieving consistency in the daily management of their dog. These are the most common reasons for insulin insensitivity.

- **Serial Blood Glucose Curve**

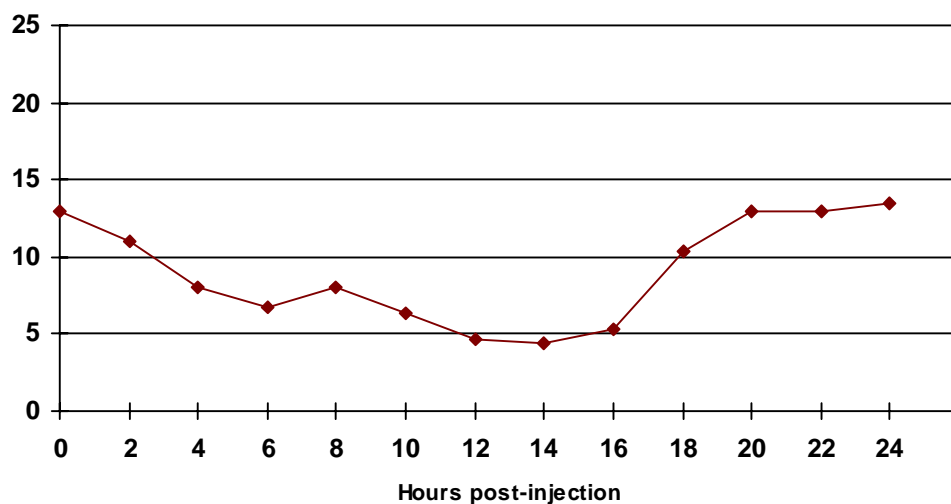
If problems are not readily apparent after evaluation of the diabetic regimen and physical examination of the dog, a serial blood glucose curve is indicated.

### *Possible Causes of Insulin Insensitivity*

<b>Insulin</b>	<b>Management</b>	<b>Endogenous</b>
Past expiry date	Inappropriate injection technique	Concurrent illnesses
Heated/frozen	Inappropriate injection site (e.g., fat)	Obesity
Vigorously shaken	Varying dose and timing of injection	Undernutrition
Antigenic	Inconsistent exercise	Hyperlipidemia
Limited duration of activity	Variable amounts and timing of feeds	Metoestrus
Inappropriately high dose	Failure to administer insulin	Use of diabetogenic drugs
Poor absorption		

### **Performing a Serial Blood Glucose Curve**

To perform a serial blood glucose curve the animal is hospitalized and the usual diabetic regimen, normally carried out by the owner, strictly adhered to. Blood samples for quantitative glucose analysis are taken every 2 hours over a 12-hour period in dogs on twice-daily insulin injections, and over 24 hours for dogs on once-daily insulin injections. The first and last injections are usually taken just prior to the insulin injection.



*24-hour blood glucose curve with reasonable control. Once-daily injection of Lente insulin, twice-daily feeding (evenly divided meals) at 0 and 6 hours post-injection. Mild hyperglycemia is expected as the effect of insulin wanes.*

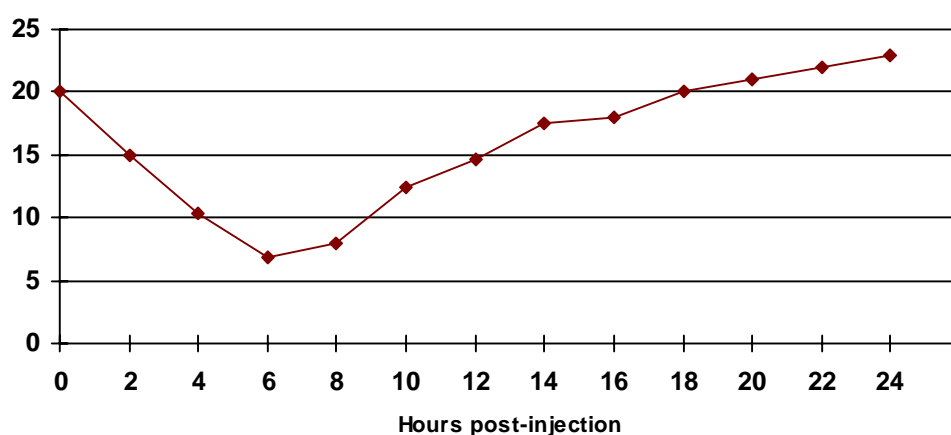
Serial blood glucose curves are of value in assessing the appropriateness of insulin injection times and doses, as well as feeding times and proportions in animals on unusual insulin regimens. However, they are more frequently performed in the investigation of insulin insensitivity where they can depict:

- Short duration of insulin activity
- Somogyi overswing
- Insulin resistance

### ***Short Duration of Insulin Activity***

The duration of intermediate and long-acting preparations may be considerably less than 24 hours in individual animals. As a result, hyperglycemia is present for significant periods of each day and may occur as soon as 6 hours after insulin injection. In animals on morning insulin injections, owners often complain about evening polyuria and polydipsia.

A diagnosis is made by demonstrating on a serial blood glucose curve significant hyperglycemia within 18 hours or less of insulin injection but without any hypoglycemia. Treatment involves changing the insulin type or frequency of injection.

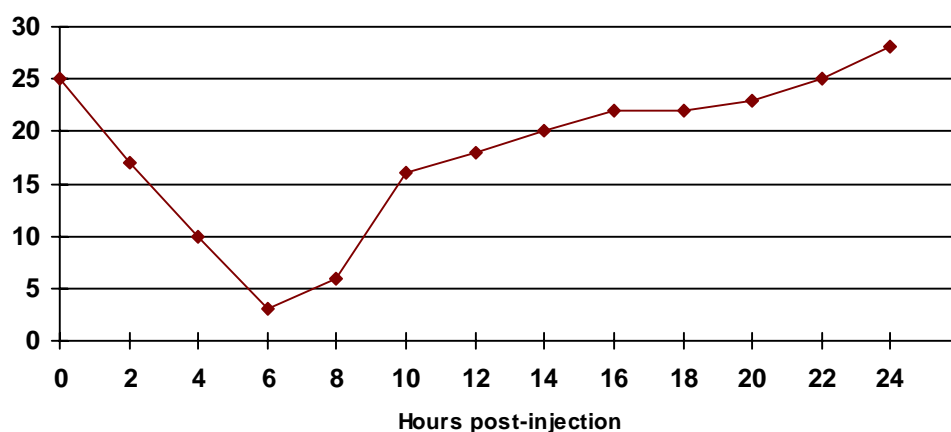


*Short duration of insulin activity. Blood glucose concentrations escape from control 8 hours following injection. Note that a “nadir” blood glucose concentration would have been within the reference range.*

### ***Somogyi Overswing***

This is a normal physiologic response to hypoglycemia that can give rise to problems in diabetic animals. Once blood glucose concentrations fall below normal, several physiologic mechanisms are stimulated which interfere with the actions of insulin and promote glucose production by the liver. In diabetic animals, insulin is not released to dampen the phenomenon and blood glucose

concentrations rise dramatically. A diagnosis is made by demonstrating on a serial blood glucose curve hypoglycemia; followed by significant hyperglycemia. It is most commonly associated with protocols using urinalysis for insulin dose adjustment. Significant morning glucosuria is automatically interpreted as an increasing insulin requirement, exacerbating the situation. Treatment is by decreasing the administered insulin dose by approximately 20% followed by re-evaluation of the patient.



*The Somogyi overswing. Hypoglycemia is followed by significant hyperglycemia. Note that the blood glucose concentration is inappropriately low at the “nadir” point.*

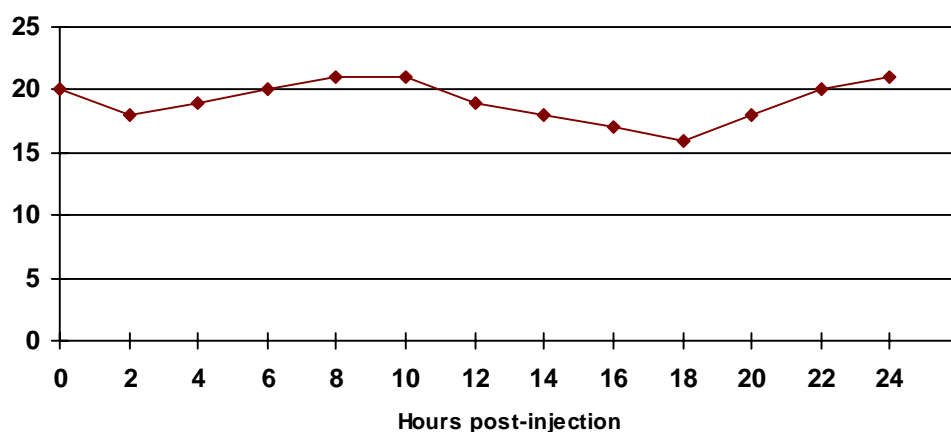
### ***Insulin Resistance***

A diagnosis of insulin resistance is made by demonstrating persistent hyperglycemia on a serial blood glucose curve, despite an insulin dose exceeding 2 IU/kg. A range of possible differential diagnoses exist, including:

- Insulin antibodies
- Poor subcutaneous absorption
- Obesity
- Undernutrition
- Metoestrus
- Hyperlipidemia
- Administration of diabetogenic drugs (e.g., glucocorticoids, progestogen)
- Concurrent illnesses:
  - Hyperadrenocorticism
  - Infection (oral/urinary/gastrointestinal)
  - Hypothyroidism
  - Renal/cardiac/hepatic insufficiency
  - Pancreatitis

- Exocrine pancreatic insufficiency
- Pheochromocytoma
- Glucagonoma

These should be systematically investigated based on clinical signs and results of supportive diagnostic tests.



*Insulin resistance. The blood glucose concentrations do not significantly decrease.*

## DIABETIC KETOACIDOSIS

Ketoacidosis is a life-threatening complication of diabetes mellitus, characterized by severe fasting hyperglycemia, glucosuria, ketonemia, ketonuria, and metabolic acidosis. Although often considered the end result of diabetes mellitus, it can easily be precipitated by an excess of such diabetogenic hormones as growth hormone, catecholamines, and glucocorticoids. For this reason, diabetic ketoacidosis is often preceded by a concurrent illness, which must be identified and treated concurrently to ensure successful management.

Ketoacidosis may also develop in animals receiving insulin therapy because of the development of other illnesses. In addition, administration of exogenous diabetogenic drugs is capable of precipitating a ketoacidotic crisis in both treated and untreated diabetic animals.

### Historical and Clinical Findings

In addition to the usual features of diabetes mellitus, ketoacidotic patients exhibit some or all of the following features:

- Depression
- Anorexia and adipsia
- Vomiting and diarrhea
- Dehydration
- Ketotic breath

Once the production and accumulation of ketones proceed, the body's buffering system becomes overwhelmed and a state of metabolic acidosis ensues. Irrespective of precipitating illnesses, accumulation of ketones results in anorexia and adipsia. Fasting promotes further gluconeogenesis and ketogenesis, and dehydration is exacerbated by the osmotic diuretic effect of both glucosuria and ketonuria and any vomiting or diarrhea that develops.

Diabetic ketoacidosis is associated with a variety of abnormalities, many of which are features of uncomplicated diabetes mellitus.

### *Laboratory Findings*

#### ***Hematology***

- Mild nonregenerative anemia (may be masked by hemoconcentration)
- Stress leukogram

#### ***Biochemistry***

- Severe hyperglycemia
- Increased liver enzymes (alkaline phosphatase [ALP], alanine aminotransferase [ALT])
- Hypercholesterolemia
- Hypertriglyceridemia
- Increased fructosamine
- Increased glycosylated hemoglobin
- Increased urea and creatinine concentrations
- $\pm$  Hyponatremia
- $\pm$  Hypokalemia
- $\pm$  Hypophosphatemia

#### ***Urinalysis***

- Glucosuria

- Ketonuria
- Evidence of urinary tract infection (protein, blood, bacteria)
- Positive urine culture if cystitis present

## Diagnosis

A diagnosis of diabetic ketoacidosis is based on the presenting clinical signs coupled with demonstration of severe hyperglycemia, glucosuria, and ketonuria.

## Management

The goals of therapy are to:

- Restore fluid and electrolyte balance and correct acidosis
- Provide insulin to suppress ketogenesis and reduce hyperglycemia
- Provide a carbohydrate substance as required during insulin therapy
- Identify and treat any precipitating/underlying factors

Overly aggressive and rapid treatment can result in neurologic dysfunction because of induced osmotic abnormalities and hypoglycemia. Thus diabetic ketoacidosis should be corrected slowly over 36 to 48 hours. Once corrected, a normal treatment regimen as for uncomplicated diabetes mellitus can be instituted. Adequate monitoring is important and is initially achieved through hourly blood glucose determinations, and electrolyte measurements as necessary.

Treatment can be successfully achieved through the following:

- Provision of intravenous fluids
- Provision of insulin
- Supplementation of electrolytes

### ***Provision of Intravenous Fluids***

Replacement and maintenance of fluid therapy is of vital importance as it serves to correct dehydration and lower plasma glucose concentrations even in the absence of insulin therapy. The initial fluid of choice is 0.9% saline, as significant deficits in total body sodium occur in diabetic ketoacidosis. Once the blood glucose concentrations reach 10 to 15 mmol/l, usually after 4 to 8 hours of fluid and insulin therapy, a 5% dextrose solution is substituted, ensuring

hypoglycemia is avoided despite continuing therapy. Adequate fluid therapy also helps correct acidosis.

Fluid requirements are based on dehydration deficits, the dog's daily maintenance requirements, and any additional losses that continue to occur because of diuresis, vomiting, and diarrhea. The maximum rate for diabetic ketoacidosis is to administer one half of the dehydration deficit over the first 2 to 4 hours and the remainder over the next 20 to 22 hours.

### *Calculating Fluid Requirements in Diabetic Ketoacidosis*

#### **Fluid Requirements**

$$\begin{array}{r} \% \text{ dehydration} \times \text{kg body weight} \times 1000 \\ + \\ 60 \text{ to } 65 \text{ ml/kg/day} \\ + \\ \text{any other losses} \end{array}$$

### ***Provision of Insulin***

Provision of insulin serves to decrease hyperglycemia, dampen ketogenesis, and correct acidosis. The use of a low-dose intramuscular soluble insulin regimen is recommended.

- 0.2 IU/kg soluble insulin intramuscularly as priming dose
- 0.1 IU/kg hourly thereafter until blood glucose concentration falls to 10 to 5 mmol/l (usually after 4 to 8 hours)
- 0.25 to 0.5 IU/kg subcutaneously or continued intramuscularly every 4 to 6 hours thereafter
- Subsequent dose adjustments by 0.5 to 1.0 IU/kg as indicated by blood glucose measurements

### ***Supplementation of Electrolytes***

Various electrolyte abnormalities are possible in diabetic ketoacidosis. Despite often-contrary laboratory evidence **hyponatremia, hypokalemia, and hypophosphatemia** usually require correction through the course of therapy.

- **Hyponatremia**

There is excessive sodium wasting in diabetic ketoacidosis because of insulin deficiency. This is exacerbated by the excessive losses induced by the osmotic diuretic effect of glucosuria and ketonuria and by any vomiting or diarrhea. Sodium is adequately replaced by using a 0.9% saline solution intravenously, at least initially.

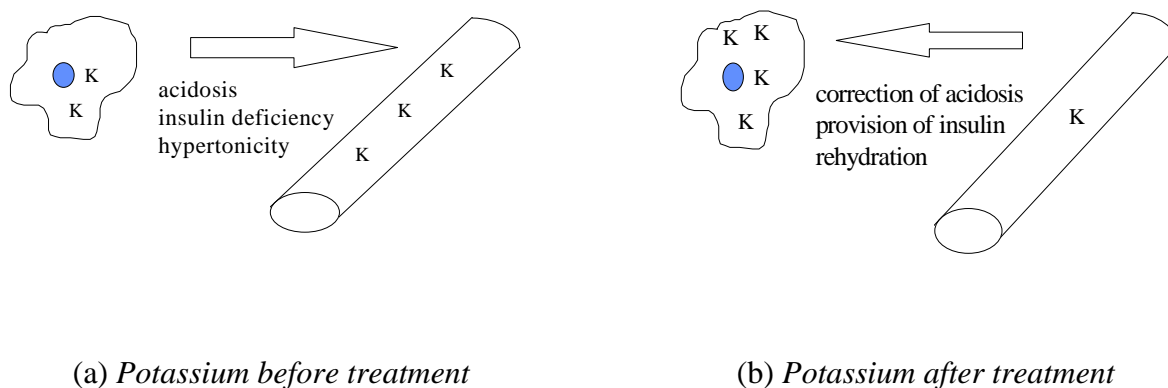
- **Hypokalemia**

Like sodium, significant body deficits of potassium exist. However, this may not be apparent on initial laboratory screening because metabolic acidosis, serum hypertonicity, and insulin deficiency promote movement of potassium into the interstitial fluid from the cells. Once treatment is instituted there can be a dramatic fall in potassium concentrations. This usually occurs within 2 to 4 hours of commencing therapy and can lead to muscle weakness and cardiac arrhythmia. Intravenous potassium supplementation will then be required.

- **Hypophosphatemia**

Like hypokalemia, hypophosphatemia may not be apparent until therapy has been instituted for 12 to 24 hours. Severe hypophosphatemia may be clinically silent, but if signs develop (hemolysis, weakness, ataxia, or seizures), intravenous phosphate supplementation is required.

### *Schematic Representation of Potassium Movement*



*Despite significant total body deficits of potassium, hypokalemia may not be apparent until treatment has commenced. Then, potassium shifts back from the interstitial fluid into the cells, resulting in obvious hypokalemia.*

## SUMMARY

Diabetes mellitus is the most common disorder associated with the endocrine pancreas. Diabetes mellitus is not a single disease, but a heterogeneous disorder of the carbohydrate, protein, and lipid metabolism. In affected patients, insulin deficiency allows glucagon-driven gluconeogenesis by the liver to proceed uncontrolled. This can be caused by autoimmune destruction of the pancreatic islets, with true insulin deficiency as a result, or as a development of impaired insulin secretion and peripheral insulin resistance. Risk factors for the latter are old age, reduced activity, and obesity.

Diabetic dogs can present with a variety of clinical signs, including polydipsia and polyuria, weight loss, and exercise intolerance. The diagnosis is based on clinical findings coupled with hyperglycemia and glucosuria as laboratory findings.

The management of diabetes mellitus is aimed at achieving adequate glycemic control and includes treatment of possible underlying conditions, the provision of insulin, appropriate dietary manipulation, and exercise modification. Insulin needs to be provided daily in order to control hyperglycemia and related problems. The appropriate insulin therapy needs to be established for each individual patient through stabilization and maintenance protocols.

The dietary management includes achieving and maintaining an ideal body weight and supporting glycemic control. Historically, it had been recommended to avoid feeding carbohydrate diets to diabetic patients, as they have difficulties in regulating blood glucose concentrations adequately. However, when using a diet high in complex carbohydrates, such as starch and fiber, the gut can act as a reservoir, slowly releasing glucose into the blood stream over an extended period of time. A diet containing a homogenous blend of soluble and insoluble fiber has been shown to be beneficial. Apart from nutrient manipulation, the appropriate feeding regimen, such as feeding meals to coincide with insulin therapy, is important.

Ketoacidosis is a life-threatening complication of diabetes mellitus, characterized by fasting, hyperglycemia, glucosuria, ketonemia, ketonuria, and metabolic acidosis. Metabolic acidosis should be corrected slowly by providing intravenous fluids and correcting possible electrolyte imbalances and providing adequate insulin.