

Managing Diabetes in Dogs and Cats



Diabetes mellitus, a common chronic metabolic disorder in middle-aged and older dogs and cats, is suspected based on a history of clinical signs and confirmed by documenting glucosuria and persistent hyperglycaemia. Diabetes management involves veterinary care and a daily routine at home that usually includes insulin administration, a consistent diet, regular exercise and monitoring. A number of intermediate- and long-acting insulin products are used successfully in the management of diabetes in dogs and cats. These products require twice-daily administration in most diabetic dogs and all diabetic cats. The aims of diabetes management include minimising or eliminating the clinical signs, avoiding hypoglycaemia and improving quality of life. Clinical remission is possible in diabetic cats. Diabetes management is about more than insulin treatment but, with teamwork, communication and monitoring, many diabetics can be managed successfully.

Diabetes mellitus is a group of chronic metabolic disorders due to defects in insulin secretion and/or insulin action that lead to resistance to the action of insulin.^{1,2} It is characterised by persistently elevated fasting blood glucose (hyperglycaemia). This causes structural and functional damage to the insulin-producing cells of the islets of Langerhans of the pancreas and insulin target tissues, which is known as glucose toxicity. In addition, there is also unrestrained production of glucose by the liver, which further contributes to the hyperglycaemia.

Diabetes mellitus is suspected based on a history of clinical signs that are likely related to the stage and severity of the disease process rather than to the cause of the diabetes.³ Clinical signs of diabetes manifest when the renal threshold for glucose reabsorption is exceeded. The presence of glucose in urine (glucosuria or glycosuria) causes osmotic diuresis and this manifests clinically as excessive urine production (polyuria) with a compensatory increase in thirst (polydipsia). Clinical signs can also include altered appetite, often accompanied by weight loss or absence of weight gain in animals with excessive appetite.^{4,5} Diabetes is most commonly seen in purebred dogs and in mixed breed cats, although some purebred cats, such as the Burmese, are at significantly increased risk.^{4,5,6,7} There does not appear to be a clear sex predilection in dogs but diabetes is most commonly reported in male neutered cats.⁴ A diagnosis of diabetes is confirmed by demonstrating glucosuria (sometimes in combination with ketonuria) and persistent hyperglycaemia.

In type 1 diabetes, there is an absolute deficiency of insulin due to immune-mediated destruction of the pancreatic cells. In type 2 diabetes, there is a relative deficiency of insulin due to an insulin secretory defect with or without resistance to the action of insulin. Type 2 diabetes is an umbrella term that is used commonly in diabetic cats. While this may be suitable classification for diabetes in obese cats, it is not a suitable term for all diabetic cats, such as those with diabetes

secondary to an endocrine condition, such as growth hormone (somatotropin) excess due to a pituitary tumour in acromegaly.⁸ Dogs were previously considered to have type 1 diabetes; however, diabetes may occur secondary to disease of the exocrine pancreas (an uncommon sequel in cats). Type 2 Diabetes can also occur in dogs secondary to endocrine conditions, such as hyperadrenocorticism (Cushing's syndrome, hypercortisolaemia) and growth hormone (somatotropin) excess, which is produced by the mammary gland during diestrus and pregnancy under the influence of the ovarian steroid hormone progesterone.⁹ The classification of diabetes in dogs and cats will likely be refined further and this will not only provide standardisation within veterinary medicine, but also likely improve outcomes by helping veterinarians to better target treatment to the underlying disease process.³

Diabetes management in dogs and cats involves veterinary care and a daily routine at home that includes insulin administration, consistent diet, regular exercise and monitoring.¹⁰ The insulin dose needed depends on the degree of deficit in insulin production and is therefore different in each case and varies with time. However, the ability of an animal to respond to a given dose of insulin (insulin sensitivity) is unknown. Moreover, many factors, including absorption from the injection site, blood glucose and insulin sensitivity at the time of treatment, and health, feeding and exercise status, impact the magnitude and response to any given dose of insulin. The majority of animals will respond to treatment with any given insulin and there is currently insufficient high-level evidence to suggest that one insulin product offers significant advantages in diabetic dogs and cats.¹¹

A number of factors require consideration, including formulation, source, concentration, and injection method and treatment frequency, when selecting an insulin product for a diabetic dog or cat. In veterinary medicine, the most commonly used insulin products are porcine insulin zinc suspension, human recombinant protamine zinc insulin and insulin glargine. Porcine insulin zinc suspension [Caninsulin®, known as Vetsulin® in the USA, MSD Animal Health (known as Merck Animal Health in the USA and Canada)], has been used successfully in diabetic dogs and cats for around 25 years.^{4,5,12,13,14,15,16,17,18,19} It contains amorphous (semilente, rapid-acting) and crystalline (ultralente, long-acting) zinc suspensions in a ratio of approximately 3:7. Human recombinant protamine zinc insulin (ProZinc, Boehringer Ingelheim) has been used successfully in diabetic cats since 2009.^{4,5,20} Insulin glargine is not approved for veterinary use but has been used successfully in diabetic cats for more than a decade.^{4,5,18,19,21}

Formulation: Insulin is inherently short-acting so, to make it suitable for use in therapy, its duration of action is increased by delaying absorption from the injection site by precipitating

insulin from solution using zinc, sometimes in combination with protamine, or by altering the structure to create a basal analogue of insulin. This also delays its onset of action and reduces its maximum blood glucose-lowering effect (for an equivalent dose). Zinc insulin crystals create a depot effect at the injection site. The absorption rate is related to the size of the zinc-insulin crystals (monomers, dimers, hexamers). Both amorphous and crystalline zinc insulin contain zinc, but amorphous insulin is more soluble in water and is absorbed more rapidly from the injection site, releasing insulin monomers into the bloodstream, than crystalline zinc insulin. Protamine is a class of basic, low molecular weight proteins with an unusually high number of arginine residues derived from fish sperm and roes. When this protein is added to insulin in addition to zinc, it helps to delay absorption from the injection site by regulating the interaction between hexamers and dimers. The addition of arginine residues to the insulin B chain in insulin glargine alters the isoelectric point of the insulin, making it more soluble at acidic pH (4.5). The neutralisation of this acidic solution in the subcutaneous tissue (pH 7.4) leads to the formation of hexamers that dissolve slowly, thus delaying the release of monomers into the bloodstream.

Source: Insulin can be animal-derived, recombinant human insulin or an insulin analogue (human insulin with an altered structure). The structure of insulin is highly conserved meaning that insulin from one mammalian species (e.g. porcine) will work in another whether the structure is identical (e.g. canine) or differs by three amino acids (e.g. feline) or more. Human (recombinant) insulin differs from canine insulin by one amino acid and from feline insulin by four amino acids.

Concentration: Veterinary-approved insulin products contain insulin at a concentration of 40 International Units per mL (40 IU/mL). This is 2.5-fold lower than is found in insulin products approved for use in humans (100 IU/mL), making it easier to measure the insulin dose required by many veterinary patients accurately, using 40 IU/mL insulin and an appropriate (U40) insulin syringe.

Injection method: Insulin is administered by subcutaneous injection and this should be performed using the corresponding size (e.g. U40) of single-use insulin syringe or an injection pen (VetPen[®], MSD Animal Health).²² Insulin pens are mechanical injection devices that are designed to deliver a set insulin dose repeatedly and accurately. They were developed to reduce the physical, cognitive, and emotional burden of diabetes management and are considered easier and more discreet to use.^{22, 23} They are also associated with improved user confidence, treatment satisfaction, and quality of life and have been shown to improve health economics through reducing the hypoglycaemia and improving adherence to insulin therapy.^{22, 23} Insulin pens dose insulin more accurately, compared to vials and syringes, since they do not rely on the ability of the user to accurately draw up the required insulin dose.^{23, 24} Improving adherence to insulin treatment to achieve better glycaemic control remains one of the challenges in the management of diabetes mellitus in dogs and cats. This type of technology offers pet owners an alternative means

of injecting insulin and it is important that the correct choice be made for each owner based on understanding their needs.

Treatment frequency: The onset, peak and duration of insulin action are not fixed as they are impacted by many factors (including absorption from the injection site, blood glucose and insulin sensitivity at the time of treatment, health status, feeding and exercise). Intermediate- (e.g. porcine insulin zinc suspension) and long-acting insulin (e.g. human recombinant protamine zinc insulin, insulin glargine) products have to be administered twice daily at 12-hour intervals to most diabetic dogs and all diabetic cats to provide adequate glycaemic control.^{4, 5, 11} It is not uncommon for a change in insulin to be made in animals where the duration of action appears to be too short. However, it is also possible to increase treatment frequency with the same insulin to improve glycaemic control and this may be both appropriate and achievable in some cases.²⁵

There are a number of goals when managing diabetic dogs and cats. The first goal is to minimise or eliminate the clinical signs of diabetes. To do this it is important that the management plan is agreed with the owner and fits easily into their daily routine.^{10, 25} The second goal of diabetes management is to avoid insulin-induced hypoglycaemia (lower than normal blood glucose). Hypoglycaemia is a serious and potentially fatal response that can occur at any stage of insulin treatment, even after an animal seems to be well-regulated, and can be precipitated by loss of appetite, gastroenteritis (particularly vomiting), or unaccustomed strenuous exercise. Pet owners should be trained to recognise signs of hypoglycaemia, such as hunger, restlessness, shivering, incoordination, disorientation, convulsions, seizures, and coma, and to seek emergency assistance from their veterinary team. A third goal is to improve the quality of life of the pet to the extent that the owner is happy with their condition.

In diabetic cats, clinical remission – the ability to maintain fasting blood glucose without exogenous insulin – appears increasingly to be a realistic therapeutic goal.^{4, 5, 11} Remission is an incidental finding in diabetic cats administered insulin twice daily with or without dietary management.^{15, 16, 18, 19} The percentage of cats going into remission approximately doubled from around one-third (2/6 insulin glargine and 8/23 porcine insulin zinc suspension) to around two-thirds or more (6/9 insulin glargine and 8/12 porcine insulin zinc suspension) when a high-protein, low-carbohydrate diet was fed in addition to the twice-daily insulin administration. (Zini, E., Tschuor F. & Reusch, C. E. (2008), personal communication) However, there is still insufficient, high-level evidence to suggest that a specific insulin or treatment regimen is more likely to lead to clinical remission and more studies are needed.¹¹ Moreover, it is also possible that higher remission rates may in fact be related to the (sub)type of diabetes that the cat has.³ Since clinical remission may be transient, it is important that these animals continue to be fed appropriately and, like all diabetics, monitored closely.

Diabetes is a chronic disease and changes in a pet's

condition can be seen with time. Close monitoring can help identify these changes promptly. Daily monitoring of diabetics at home can include a number of parameters that indirectly or directly reflect blood glucose concentrations, such as measuring water intake, assessing urine output (e.g. weighing the cat's litter box, frequency of nocturia in dogs) or blood glucose measurement.¹⁰ It is important that the pet owner keeps a record of significant findings at home and that this record, whether it be a diary, calendar, spreadsheet or app, such as Pet Diabetes Tracker, is made available to the veterinary team for review.¹⁰ Diabetes management is about more than insulin treatment but, with teamwork, communication and monitoring, many diabetics can be managed successfully.

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