

# DIABETES IN DOGS AND CATS – AN UPDATE.

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There are actually two major forms of diabetes: *diabetes insipidus* and *diabetes mellitus*. Diabetes insipidus (DI) is a term used to describe the obligatory passage of large volumes of extremely dilute urine, usually with a consequent increase in thirst and water intake. DI has many causes. It may result from a failure of production of antidiuretic hormone (vasopressin) by the hypothalamus or a failure of the kidney tubules to respond appropriately to vasopressin. Drugs, infections, hormones, and hypercalcaemia can interfere with the action of vasopressin on the kidney tubules. Typically, the urine of patients with DI does not contain sugar and would not taste sweet (if you unwisely chose to taste it!).

The word 'diabetes' is often used synonymously with diabetes mellitus (DM) or 'sugar diabetes'. *Mellitus* means sweet and DM gets its name from the fact that the urine of patients with this disease would taste sweet, whereas the urine of patients with DI would taste bland or insipid.

Diabetes mellitus is a large and important topic. Therefore, in the remainder of these notes, I shall consider selected aspects of diabetes mellitus in which there has been some recent progress.

## **Aetiology / Pathogenesis**

The pancreas has endocrine and exocrine components. The endocrine pancreas consists of numerous small islands of endocrine tissue (the islets of Langerhans) surrounded by a 'sea' of exocrine glandular tissue that produces digestive enzyme precursors for secretion into the intestines. The islets of Langerhans contain several different kinds of hormone-secreting cells; the ones most relevant to this talk are the *beta cells*, which secrete insulin. DM is the most important disease of the endocrine pancreas in dogs and cats. It arises from an absolute or relative deficiency of insulin secretion by the beta cells of the islets of Langerhans.

In humans, DM is categorised into four main types. These are type 1, type 2, gestational and other. Type 1 is thought to be the most important category in dogs, affecting at least 50% of dogs with DM.[1] Type 1 DM is essentially an autoimmune disease. There is immune destruction of the beta cells in the islets of Langerhans. Some dogs are genetically

predisposed to this immune destruction, so certain breeds are overrepresented and affected individuals may even have a family history of DM.

Pancreatitis is another important cause of canine DM in the 'other' category, reported to cause DM in 28% of cases. Actually, this may be an underestimate since chronic, smouldering pancreatitis can be difficult to diagnose. During bouts of pancreatitis, which may be clinically unapparent, inflammation originating in the exocrine pancreas destroys the embedded islets. It is also possible that pancreatic inflammation predisposes to the development of autoimmunity against beta cells. Eventually, enough islets are destroyed to cause overt DM. Obesity predisposes dogs to develop pancreatitis, and so indirectly it may predispose some dogs to develop DM. Evidence that obesity *directly* predisposes dogs to develop DM is lacking. Indeed, there is no convincing evidence that type 2 DM is a significant disease entity in dogs.

Some bitches may suffer from the equivalent of gestational diabetes during pregnancy and dioestrus, but this is relatively uncommon.[2] Progesterone stimulates growth hormone to be produced by the canine mammary gland. Growth hormone induces a high degree of insulin resistance. Numerous endocrine diseases and drugs can interfere with the actions of insulin, causing so-called insulin resistance. Glucocorticoid therapy (e.g., with prednisolone), progestational drugs, hyperadrenocorticism and acromegaly (growth hormone excess) all cause insulin resistance and can predispose to DM. If a dog has concurrent islet damage, for example as a result of pancreatitis or immune destruction of beta cells, then DM is all the more likely to develop.

Type 2 DM, sometimes described as non insulin-dependent diabetes mellitus (NIDDM) is thought to be the most important type of DM in cats. As in people, this form of diabetes is associated with obesity and physical inactivity and can sometimes be managed without the need for insulin injections. In type 2 DM, there is insulin resistance (*i.e.*, a lack of insulin glucose-lowering effectiveness in the target tissues) and an insufficient compensatory increase in insulin secretion by the beta cells. Nevertheless, in type 2 DM it is often the case that the islets remain capable of producing some insulin. The amount of insulin produced, and the extent of insulin resistance, vary over time. Sometimes insulin production dwindles as the disease progresses, but it may be able to rebound if blood glucose concentrations can be brought sufficiently under control. This helps to explain the fact that feline diabetes is often transient, going into "remission" with treatment. It also helps to explain why treatments other than insulin injections (e.g., dietary management, increased exercise and oral hypoglycaemic drugs) can sometimes be effective in cats and people with type 2 DM. Type 2 diabetes is not the only type of DM in cats. As in dogs, pancreatitis can cause DM and may be under-diagnosed. Pancreatitis in cats can be very difficult to

diagnose. Pancreatic cancer (adenocarcinoma) is another cause of islet destruction and DM. Pancreatic amyloid accumulation often occurs in cats with DM, but it is unclear whether this is a cause or consequence of feline DM, or both. Cats also suffer (albeit infrequently) from acromegaly and hyperadrenocorticism, both of which can cause DM in cats. Hyperthyroidism tends to cause more modest insulin resistance.

To complicate matters, the distinction between IDDM and NIDDM is not hard and fast. Prolonged hyperglycaemia of any cause can diminish the ability of the beta cells to produce insulin, either temporarily or permanently. This sometimes reversible effect of prolonged hyperglycaemia is called 'glucose toxicity'. One would usually expect an endocrine tissue to hypertrophy when stimulated. Unusually, when beta cells are stimulated to secrete a large amount of insulin over a period of time they may sustain damage and undergo programmed cell death. So an obese cat starting with insulin resistance (NIDDM) and high blood insulin levels may eventually become completely dependent upon insulin injections and incapable of producing any insulin from its islets.

An excellent article entitled "*Canine and Feline Diabetes Mellitus: Nature or Nurture*" by Jacquie Rand and her colleagues at the University of Queensland [1] was published in the Journal of Nutrition fairly recently and is well worth a read.

## **Epizootiology**

The incidence of feline diabetes mellitus has been estimated at 0.25-2%. In the UK, the incidence of canine DM has been estimated at 0.32%. There is some evidence that these incidence rates may be increasing. For the cats, this may in part be because more of them are obese and doing less exercise.

In both dogs and cats, DM tends to be diagnosed in middle-aged to older animals. Infrequently, DM is diagnosed in young animals less than a year of age. Neutering and being male are other risk factors for feline DM. Conversely, bitches are affected twice as often as male dogs.

Burmese cats are reported to be much more prone to develop DM than are other breeds in Australia, New Zealand and the UK. The same may hold true in other parts of the world. In some parts of the world, 1 in 50 Burmese cats reportedly has DM and a staggering 1 in 10 Burmese cats over 8 years of age has the disease! Cavalier King Charles Spaniels, Samoyeds, Schnauzers, Australian terriers, miniature poodles, Rottweilers and Bichon frise are among the canine breeds reported to have a high risk of developing DM, whereas German shepherds, collies, Golden retrievers and Labrador retrievers are at much lower risk than other breeds.

Interestingly, canine DM is diagnosed more frequently in the winter months than in the summer. Whether this reflects closer observation of dogs by owners during the winter, different behaviour of dogs during colder weather, or a genuine seasonal variation in the onset or progression of pancreatic pathology is uncertain.

## **Diagnosis**

Diagnosis is based on signalment, history (polyuria, polydipsia, polyphagia, weight loss), physical examination findings and the presence of persistent fasting hyperglycaemia with glucosuria. The presence of ketonuria confirms diabetic ketosis or ketoacidosis. Usually, no attempt is made to distinguish IDDM from NIDDM at initial presentation. That distinction may only become apparent weeks or months later.

A thorough diagnostic investigation is important in diabetic patients because often there are other, concurrent illnesses that may affect the response of the patient to management of its DM. For example, urinary tract infections are common in patients with DM and may cause stress, inducing a degree of insulin resistance and affecting (*i.e.*, diminishing) the responsiveness of the patient to insulin therapy. A thorough diagnostic investigation may also reveal an underlying cause for insulin resistance, such as hyperadrenocorticism.

In non-neutered bitches, the possibility of gestational or dioestrus DM should be considered. A pragmatic approach is to offer to neuter intact bitches and see whether the DM resolves.

## **Monitoring**

There are some fairly new tools for monitoring diabetic dogs and cats, but the mainstays remain the history and physical examination (including body weight and condition score). Assessment by the owner of the animal's water intake is particularly important. The owner should also be questioned about the animal's overall health and energy levels. Because cats are so prone to stress hyperglycaemia, micromanagement is to be discouraged and in-hospital serial blood glucose curves reserved for initial stabilisation and, later on, for situations where there is a perceived need to adjust insulin therapy.

At-home daily urine glucose measurement is unnecessary in many well-managed diabetic patients. Occasional monitoring is useful in the following situations: a). to detect ketonuria or persistent absence of glucosuria (possibly indicating insulin overdose); b). in cats that are in DM "remission", to check for recurrence of glucosuria; and c). in cats receiving oral hypoglycaemic drugs, to check whether the degree of glucosuria has improved or worsened.

The adjustment of insulin dose based on morning urine glucose concentration is to be discouraged. Records of morning urine glucose concentrations can help to inform decisions

about insulin dose adjustments, but daily changes based on morning urine glucose concentrations more often lead to difficulties.

Urine can be collected from litter trays if the normal litter is temporarily replaced with aquarium gravel. Alternatively, there are commercially available urine glucose paper test squares that can be mixed with litter (Glucotest™ Feline Urinary Glucose Detection System; Ralston Purina).

Fructosamines are proteins to which glucose has been irreversibly and non-enzymatically bound. Serum fructosamine concentration gives an indication of the mean blood glucose concentration over the last several (1-3) weeks. Stress hyperglycaemia, which is very short lived, does not affect serum fructosamine, but fructosamine may be abnormally low in hypoproteinaemic cats and hypoalbuminaemic, hyperlipidaemic and azotaemic dogs. Serum for fructosamine measurement should be separated, frozen and submitted to the laboratory on cold packs. It can be used for diagnosis of DM and for monitoring patients under treatment for DM. Unfortunately, some dogs and cats whose diabetes seems to be very well controlled have abnormally high or low serum fructosamine concentrations.

At-home serial blood glucose curves can be generated by owners who are dextrous and willing to prick the marginal ear veins (or paw pads) of their cat. Such owners are usually motivated enough to buy their own portable glucometer. An excellent Web-based resource is available, so that owners can decide whether or not they are willing to attempt this procedure (<http://www.sugarcats.net/sites/harry>). It should be borne in mind that many portable glucometers generate results that are different (often lower) than reliable reference methods. In general, the further the blood glucose is from normal, the less reliable is the result.

Recently, a continuous glucose monitoring system has been assessed for use in diabetic dogs.[3] Such systems allow for continuous, minimally invasive glucose monitoring. A glucose sensor is implanted subcutaneously using a 22-gauge needle attached to a spring-loaded device. The sensor can remain in place for up to 72 hours. Interstitial fluid glucose concentrations are measured every few seconds and an average value is reported every five minutes. The sensor and monitor work very much along the lines of a Holter ECG monitor, very portable. Unfortunately, several blood samples need to be taken during each 24-hour period, so that the subcutaneous glucose sensor can be properly calibrated. The device may not measure low blood glucose concentrations as reliably as it measures normal and high ones. Nevertheless, this new technology holds great promise for monitoring diabetic animals at home and in the hospital. Unfortunately, it is for the moment very expensive.

## Treatment

Oral hypoglycaemic drugs (e.g., glipizide, glimiperide) are best reserved for cats whose owners would choose euthanasia rather than administering insulin injections. A few weeks of extra time may allow owners to come to terms with their cat's diabetes and change their minds about learning how to carry out the insulin injections.

Insulin glargine (Lantus®) is a relatively new human synthetic insulin analogue produced in *E. coli* bacteria using recombinant DNA technology.[4] The amino acid sequence differs from ordinary human insulin at three positions. Glargine is a clear and colourless solution, not a suspension like other long-acting insulins. It contains 100U/ml insulin and should not be diluted before injection. This is because it is specially formulated to be at pH 4, and dilution with most commonly available diluents would change that. When pH 4 glargine is injected, and encounters pH neutral subcutaneous tissues, microprecipitates form immediately. From these, insulin is released gradually over a long period. This is the basis of its long-lasting "peakless" effect when used in diabetic people. Recent work using glargine in cats has provided very promising results. Glargine has a long-lasting effect in cats. Nevertheless, it seems to work best when it is administered twice daily. Although it is quite expensive, it seems to be able to send many cats into "remission". When this happens, the overall cost is less for the owners than when using more conventional insulins.

## References / Further reading

1. Rand, J.S., L.M. Fleeman, H.A. Farrow, D.J. Appleton, and R. Lederer *Canine and feline diabetes mellitus: nature or nurture?* Journal of Nutrition, 2004. **134**(8 Suppl): p. 2072S-2080S.
2. Norman, E.J., K.J. Wolsky, and G.A. MacKay *Pregnancy-related diabetes mellitus in two dogs.* New Zealand Veterinary Journal, 2006. **54**(6): p. 360-4.
3. Davison, L.J., L.A. Slater, F. Gaudiano, D.B. Church, M.E. Herrtage, J.M.E. Ristic, and B. Catchpole *Use of the medtronic minimed continuous glucose monitoring system for assessment of diabetes mellitus in 40 dogs.* Journal of Veterinary Internal Medicine, 2006. **20**(3): p. 727-727.
4. Norman, E.J. *Glargine - A new synthetic insulin.* Companion Animal Society Newsletter, 2005. **16**(3): p. 22-26.