B37
FELINE DIABETES MELLITUS: HOW RELEVANT ARE ACROMEGALY, HYPERADRENOCORTICISM AND PANCREATITIS AS UNDERLYING DISORDERS?
Claudia E. Reusch, Dr. med.vet, Prof., DECVIM-CA
ZURICH, SWITZERLAND

INTRODUCTION
Traditionally, the classification of diabetes mellitus in cats has more or less followed the model used in human medicine. Although the etiopathogenic mechanisms may not be identical, the human model provides a guide for the characterization of various forms of the disease. While type-1-like diabetes seems to be rare it is currently assumed that up to 80% of cats suffer from a type-2-like diabetes. Other specific types (formerly called secondary diabetes mellitus) may occur in approximately 20% of diabetic cats. They develop as a sequela of another disease, the most important of which are pancreatitis, hyperadrenocorticism and hypersomatotropism (acromegaly). Diabetes may also be drug-induced (glucocorticoids, progestins). Usually, the presence of those diseases is only considered in cats in which regulation of diabetes is difficult.

WORK-UP IN DIABETIC CAT WITH PERSISTENCE OF CLINICAL SIGNS
Recurrence or persistence of clinical signs is a frequent problem in diabetic cats. The first step is to confirm that the cat is indeed poorly regulated (i.e. has clinical signs of diabetes). High blood glucose levels may be incorrectly interpreted to be the result of poor glycemic control when, in fact, they are stress induced. Fructosamine concentration is also not always a reliable parameter and is sometimes moderately to markedly increased although the cat is clinically well.

In cats in which the insulin dose has been increased to approximately 1 U/kg BID a stepwise approach should be taken to exclude technical errors, insulin underdose, insulin overdose and Somogyi effect, short duration of insulin effect or prolonged duration of insulin effect. If no problem is identified thus far diagnostic work-up for diseases causing insulin resistance should be pursued. In principle any other concurrent disease (e.g. inflammatory, infectious, neoplastic) may cause insulin resistance. The most relevant are: pancreatitis, hyperadrenocorticism, hyperadrenocorticism, hypersomatotropism, infection of oral cavity, chronic renal failure and obesity. As a last resort, poor absorption of insulin and circulating insulin antibodies should be considered, although the relevance of the latter is controversial.1 The review will focus on pancreatitis, hyperadrenocorticism and hypersomatotropism.

HYPERADRENOCORTICISM
Approximately 80% of cats with hyperadrenocorticism (HAC) will develop diabetes mellitus. Insulin resistance is often severe, however, there are cases with only mild or moderate insulin resistance. HAC is considered to be a rare disease in cats. 75 – 80% of cats have pituitary-dependent disease and 20 – 25% have cortisol-secreting adrenocortical tumors. In rare circumstances, adrenocortical tumors secrete other steroid hormones (e.g. progesterone). However, clinical signs are identical to those of hypercortisolism, and diabetes mellitus may develop as well. In addition to pu/pd and weight loss, which are usually due to concurrent diabetes mellitus, typical clinical signs are abdominal enlargement, an unkempt seborrheic hair coat, thinning of the hair coat, failure of hair to regrow or alopecia and muscle weakness. Severe cases may have thin fragile skin that tears easily. Cats with large pituitary masses may have CNS disturbances. However, clinical signs may also be mild and HAC is often not suspected until it becomes evident that the diabetes is difficult to regulate.

As in dogs the work-up is a two step procedure. First, the diagnosis of HAC should be confirmed by means of screening-tests. The urine cortisol-to-creatinine ratio has been described to be a sensitive screening-test. It should be remembered that reference values are strongly laboratory/assay dependent, and that the test’s specificity is only moderate. We recently investigated the dexamethasone test in a group of diabetic cats 6 weeks after initiating insulin therapy. In 20 of 22 cats, the cortisol concentration was completely suppressed at 4 and 8 hours after the application of 0.1 mg/kg dexamethasone IV. The results did not differ between cats with good glycemic control and those with moderate to poor control. In 2 cats, the test was abnormal and hyperadrenocorticism was confirmed by histopathology.2 Based on our results, the dexamethasone test appears to be a suitable part of the diagnostic work-up in diabetic cats suspected of having hyperadrenocorticism. In our hospital, the test is carried out 6 – 8 weeks after initiating insulin therapy. The ACTH stimulation test is a test to investigate adrenal reserve, and therefore a test which is more appropriate for the diagnosis of hypo- than hyperadrenocorticism. Ultrasonography may be used as a discriminating test, whereas, interpretation of the adrenal gland findings appear to be more difficult than in dogs.
general terms bilateral symmetrical appearance of the adrenal glands in cats with confirmed HAC is indicative for pituitary disease, unilateral enlargement or differences in size for an adrenal tumor. Further discriminating tests are measurement of endogenous ACTH and pituitary imaging by means of CT or MRI.

Treatment of feline HAC is difficult and none of the treatment modalities have been used in a large enough number of cats to allow reliable recommendations. Microsurgical transphenoidal hypophysectomy is an effective method, and may become the treatment of choice in the future. Currently, expertise is lacking in most centres. Pituitary radiation has been described in only very few cats with mixed results. Bilateral adrenalectomy has long been considered the treatment of choice, however post surgical complications are common and lifelong treatment with mineralo- and glucocorticoids is required. The response to medical treatment as mitotane or ketokonazole has been poor. Recently, trilostane has been used with some success and may become the medical treatment of choice. Initial dosage usually is 30 mg/cat SID. In cats with unilateral adrenal tumor removal of the affected gland should be recommended.

**HYPERSOMATOTROPISM (ACROMEGALY)**

Nearly all cats with hypsomatomatotropism will develop diabetes mellitus. Hypersomatotropism in cats is caused by a growth hormone (GH)-producing tumor (usually an adenoma) in the pars distalis of the pituitary gland. GH has catabolic and anabolic effects; the latter are in part mediated by insulin-like growth factor-I. The catabolic effects are mainly due to insulin antagonism and are the reason for the diabetes mellitus. The anabolic effects include proliferation of bone, cartilage, soft tissue and organs resulting in a large body size, broad head and large paws, weight gain, prognathia inferior, respiratory difficulties because of thickening of pharyngeal tissues, degenerative arthopathy and organomegaly with potential organ dysfunction. Growth of the tumor may lead to signs of CNS disease. As previously mentioned for hyperadrenocorticism, clinical signs may also be very subtle or even absent.

Acromegaly has long been considered a rare disorder. It was recently suggested that acromegaly occurs more frequently than previously thought and is most likely underdiagnosed. However, more studies are needed to evaluate the true incidence of the disease. According to currently available data it seems that acromegaly is relatively frequent in cats with insulin resistance but uncommon in uncomplicated cases. Since the availability of a validated GH assay for cats is a problem, diagnosis is usually based on the finding of high IGF-1 concentration. Two important points should be kept in mind. First, circulating IGF-1 is bound to proteins, which must be removed before measurement. However, not all methods are equally effective, and intra-assay inference of binding proteins may lead to false high IGF-1 levels. Therefore, only assays validated for the cat should be used. Second, IGF-1 concentrations are often low in newly diagnosed diabetic cats and increase markedly after initiating insulin therapy. Low IGF-1 levels have also been seen initially in untreated diabetic cats with acromegaly. This observation is explained by the fact that relatively high insulin concentrations are required in the portal vein for the expression and function of GH receptors on hepatocytes, and this mechanism is impaired in insulin-deficient states. In our hospital, IGF-1 is therefore usually only measured 6 – 8 weeks after initiating insulin therapy.

Experience with treatment is limited. As in cats with hyperadrenocorticism microsurgical transsphenoidal hypophysectomy may become the treatment of choice at some time in the future. The most frequently reported modality currently is radiation therapy. We and others have seen clinical improvement, reduction of insulin requirement and decrease in size of the pituitary tumor. Interestingly, IGF-1 does not seem to be a suitable method to monitor treatment success, i.e. it may remain high despite improved glycemic control. Medical treatment with somatostatin analogues may be successful in some cases.

**PANCREATITIS**

The association between diabetes mellitus and pancreatitis is complex and far from being clear in humans as well as in small animals. Although the endocrine and exocrine pancreatic tissues have traditionally been viewed as separate systems it is now clear that they are anatomically and functionally related. There is cell-to-cell contact between exocrine and endocrine cells and an islet-acinar portal system communicates between the two parts. It is assumed that blood coming from the islets flows into the acinar capillaries before leaving the pancreas and that islet hormones have a role in regulating the exocrine pancreas.

In humans it has long been thought that diseases of the exocrine pancreas account for about 0.5 – 1.7% of all cases of diabetes. However, recent papers suggest that the prevalence is underestimated and may in fact comprise 8% or more. In around 50% of human patients with acute pancreatitis temporary hyperglycemia can be observed, diabetes may persist in 1 – 15% of them. In chronic pancreatitis the prevalence of diabetes varies between 30 and
83%. The longer the duration of chronic pancreatitis the higher the number of patients who develop diabetes. To make the issue even more complex it is now known that approximately 40% of patients with type 1 and type 2 diabetes have impaired exocrine pancreatic function.14

In diabetic cats pancreatitis may also be common, however, it is not known whether the former triggers the latter or vice versa. In one retrospective post mortem study pancreatitis was present in 19 of 37 (51%) diabetic cats (chronic pancreatitis in 17, acute-subacute in 2).15 In a recent laboratory study increased fPLI was found in 24 of 29 (83%) samples from diabetic cats. Unfortunately nearly no clinical information was available due to the nature of the study (evaluation of submitted samples). Interestingly in the same study fPLI was also increased in 15 of 23 (66%) of samples from non-diabetic cats.16 We are currently investigating the relationship between pancreatitis and diabetes mellitus and the various diagnostic tests in a prospective manner. In cats with newly diagnosed diabetes without any obvious complications the prevalence of increased fPLI is much lower than in the study mentioned above. Only 2 out 13 (15%) cats had mildly increased fPLI (between 12 and 20 µg/dl), in all other cases it was normal.

Clinical signs of pancreatitis are unspecific and may range from mild to life-threatening. The most common signs are anorexia, lethargy, less common are vomiting and diarrhoe. Others such as tachypnoe/dyspnoe, hypothermia or fever, tachycardia, abdominal pain and a palpable abdominal mass may also be seen. Glycemic control can be extremely difficult in cats with pancreatitis and glucose concentrations may show wide fluctuations with unpredictable episodes of hypoglycaemia. Treatment of acute pancreatitis includes fluid therapy, pain management, antiemetics, nutrition, antithrombotic prophylaxis, antibiotics. In chronic pancreatitis treatment is mainly limited to dietary management.

REFERENCES