The Secrets to Managing Problem Diabetics Mini Series

Session Two: Recognising and Managing Underlying and Concurrent Disease

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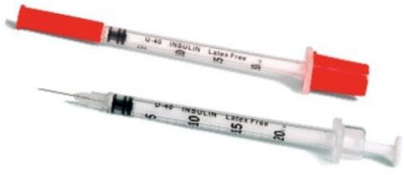


Study notes Session 2 - Recognising and managing underlying and concurrent disease

Introduction

Some diabetic cases go like a dream but many are a real headache require considerable input of time and energy with many being a marathon rather than a sprint. This 3 part webinar mini-series aims to look at the potential causes, how they can be recognised and solutions that might be available. In the speaker's experience more problems are related to insulin dose, especially over-swing and fewer to intercurrent disease than previously suggested.

This second session is focused on recognising and managing underlying and concurrent disease in order to improve diabetic stability and response to treatment.

Whilst it is important to remember that many cases of unstable diabetes are solely due to injection technique, insulin storage, management consistency, dose, type and timing of insulin given; there are a significant number of cases in which the patient may have an underlying or concurrent disease. Such disease states need to be recognised and their impact on the patient's diabetic stability assessed. They may also require appropriate management in their own right.

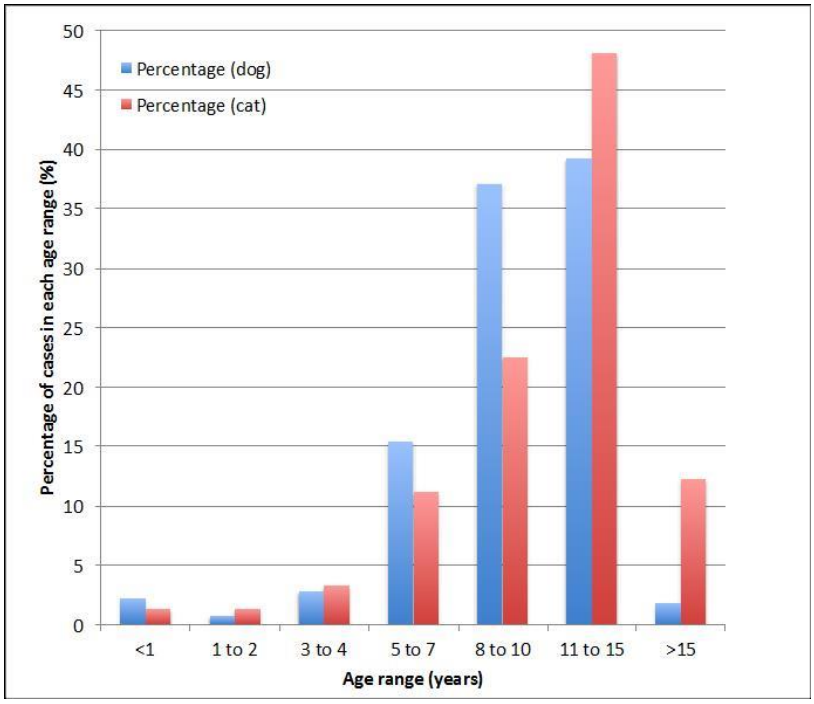
Concurrent disease complicating diabetic management are common and occur in around 70% of DKA cases. Most chronic complications in man such as cardiovascular disease and nephropathy take years to develop and are uncommon in diabetic dogs and cats. For example although diabetic nephropathy is recognised histologically, clinically significant disease is uncommon and in many cases may be a comorbidity as diabetes is prevalent in older patients, some level of independent CKD is relatively common. When faced with a poorly responsive diabetic, where underlying/concurrent disease may be a problem then a logical approach is important (Box 1) – order of testing will to some extent depend on history and other clinical signs. As diabetes is seen most commonly in older dogs (Guptill *et* al 2003) and cats (Prahl *et al* 2007) (Fig. 1) comorbidities are common making it difficult to assess, in some cases, whether such comorbidities are due to the patient also being diabetic or that diabetic instability is due to the comorbidity(ies) diagnosed.

A list of recognised causes of insulin resistance is given in table 1.

Comorbidity	Diabetes related
• Hypertension • Acromegaly • Pancreatitis • Hyperadrenocorticism • Urinary tract infection • Hypothyroidism • Hyperthyroidism • Chronic kidney disease • Dermatitis/otitis	• Cataracts • Anterior uveitis • Retinopathy • Diabetic neuropathy • Diabetic nephropathy • Urinary tract infection

Box 1 – Diagnostic approach for evaluating insulin resistance
Haematology, biochemistry (include lipid levels) and urinalysis (include culture & UPC)
Serum pancreatic lipase
Serum TLI (dogs)
Adrenal function testing
Thyroxin level (cats) thyroid function (dogs)
Reproductive cycle stage (entire female dogs) – progesterone or vaginal cytology
Abdominal ultrasound – liver, kidneys, adrenal glands, bladder, pancreas
Thoracic radiography – neoplasia, cardiomegaly
Echocardiography – evidence of significant cardiac disease on physical examination/thoracic radiographs
Advanced imaging – pituitary mass, inflammatory or neoplastic CNS disease

Figure 1 - Age of onset of diabetes in dogs and cats

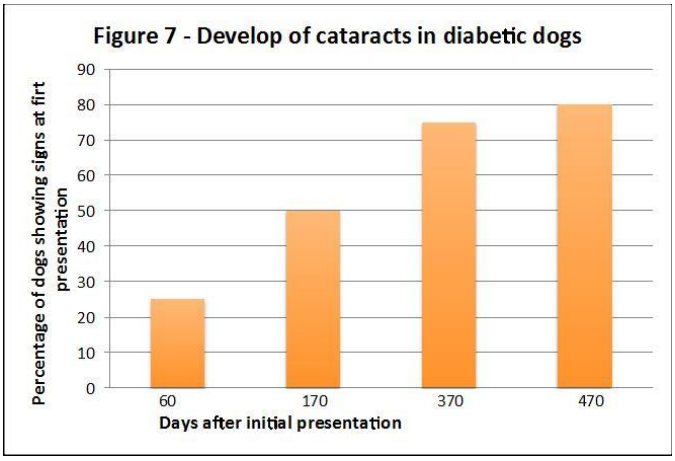


NB1 - Age of onset is slightly older in cats than dogs
NB2 - 83% cats > 8 years old
NB3 - 78% dogs > 8 years old

Table 1 - Recognised diseases causing insulin resistance

Disorders causing severe insulin resistance	Disorders causing variable insulin resistance	
Hyperadrenocorticism	Obesity	Disease of oral cavity
Dioestrous	Infection	CKD
Acromegaly	Chronic inflammation	Hepatobiliary disease
	Chronic pancreatitis	Cardiovascular disease
	Inflammatory bowel disease	Hypothyroidism
	Glucagonoma	Hyperthyroidism
	Phaeochromocytoma	Pancreatic insufficiency
	Neoplasia	Hyperlipidaemia

Diabetic cataracts, anterior uveitis and retinopathy



Diabetic cataracts - Cataracts are the most common complication in diabetic dogs with 75% of dogs having evidence of cataracts at the time of diagnosis of which 80% of dogs have developed clinically significant cataracts within 18 months (Fig 2). The pathogenesis of cataracts is thought to be due to the accumulation of sorbitol and galactitiol within the lens leading to swelling and rupture of the lens fibres. Cataract formation seems to be irreversible once it has begun and can develop rapidly (weeks) in some dogs. Traditionally it has been felt that diabetic control does not strongly influence the formation but careful questioning of most owners does seem to demonstrate that a period of diabetic instability precedes progression. Cataract surgery is required and currently phacoemulsification is the treatment of choice if electroretinography has demonstrated reasonable retinal function. Vision is restorable in about 80% of dogs (Appel *et al* 2006) but a percentage will develop complication that may occur a long time post surgery e.g. glaucoma. Surgical success is influenced by degree of glycaemic control prior to surgery, presence of retinal disease or lens-induced uveitis. The risk of developing post-operative complications is also affected by a number of other factors including breed with Labradors being at particular risk of developing glaucoma following phacoemulsification (35% vs 9% at 2 years post surgery) (Moeller *et al* 2011). A recent study has suggested that melatonin may be useful in reducing post-operative inflammation following phacoemulsification particularly in diabetic patients (Sande *et al* 2016).

Keratoconjunctivitis sicca is approximately twice as common in diabetic dogs following phacoemulsification for cataracts than non-diabetic dogs hence tear production should be closely monitored following surgery.

Lens-induced uveitis

Restoration of vision has a high success rate but long term complications can arise due to lens induced retinitis associated with lens rupture or reabsorbing hypermature cataracts. Treatment of uveitis is primarily based on reducing the inflammation that requires at least topical glucocorticoids that can have systemic affects increasing insulin resistance. If side effects are unacceptable ocular NSAID or ciclosporin can be used. Poorly controlled uveitis can lead to long term consequences such as glaucoma and eventually requiring enucleation.

Corneal ulceration

Diabetic dogs have a significant reduction in corneal sensitivity and are therefore at increased risk of corneal injury.

Diabetic retinopathy

Overall diabetic retinopathy is uncommon in dogs. The condition is associated with degeneration of eth retinal ganglion cells and is seen as retinal haemorrhage and microaneurism. Ideally electroretinography should be performed prior to cataract surgery.

Cataracts in cats

Clinically significant cataract formation is uncommon in cats although some degree of lens opacification is present in 96% of diabetic cats with about half of these likely to have some reduction in their vision. More severe cataract formation with the potential for blindness can occur in kittens due to higher levels of aldose reductase in the lens of young cats.

Hypertension

It is estimated that around 25% of diabetic cases are hypertensive although some studies have suggested that this figure may be higher towards 60% taken as longitudinal data measured over 2 years in a small group of 11 dogs 55 and 64% showed a least one episode of systolic or diastolic hypertension. In a study of 50 dogs (Struble *et al* 1998), hypertension was detected in 23 on the basis of a systolic pressure > 160 mm HG (12 dogs), a diastolic pressure > 100 mm HG (21), or a mean pressure > 120 mm HG. Ten of 12 dogs re-evaluated at subsequent visits had no change in blood pressure.

The significance to the patient and in terms of diabetic control is unclear as no correlation has been shown between glycaemic control and the risk of hypertension. The cause is also unknown but may relate to subclinical diabetic nephropathy.
Hypertension would appear to be uncommon in diabetic cats and the incidence similar to that in age matched controls. Isolated cases are described where the presence of hypertension may be of clinical significance.

Acromegaly in cats
Much debate persists around the prevalence of acromegaly in diabetic cats and indeed whether all acromegalic cats are diabetic. An estimate of around 10% of diabetic cats is probably reasonable although some authors have suggested a prevalence of 25% (Niessen *et al* 2015) although this seems at variance to the levels of diabetic remission that are reported. Clinical signs of acromegaly are listed in Box 2 but are very variable with some acromegalic cats showing no outward signs. Ultrasound examination of the abdomen of diabetic cats has associated the presence of hepatomegaly and bilateral adrenomegaly as being a sign of an acromegalic diabetic. Acromegalic cats tend to have larger pancreases and kidneys. Acromegalic cats had an enlarged renal length (>43mm) in 82% of left and 73% of right kidneys compared to 21% and 38% of non-acromegalic diabetic cat kidneys (Lorenco *et al* 2015). Acromegaly is investigated using insulin insulin-like growth factor (IGF)-1 measurement. IGF-1 is heavily protein bound and removal of protein binding is a key step in the analysis and inadequate removal of binding proteins can lead to falsely high IGF-1. IGF-1 concentrations tend to be low in newly diagnosed diabetics so testing should be delayed until 6-8 weeks after starting insulin therapy. In insulin-deficient states, GH receptors on hepatocytes are down regulated resulting in decreased production of growth hormone and therefore IGF-1. IGF-1 levels over 1000ng/ml are considered supportive of a diagnosis of acromegaly with around 90% of cats with IGF-1 above 1000ng/ml having imaging evidence of a pituitary mass. Managing diabetic acromegalic cats is difficult as their insulin requirement is variable depending on the level of IGF-1 production. As a result hypoglycaemic crises are common. Surgery offers the best long term outcome for acromegaly but is expensive and there are appreciable post operative risks; current success rates in the UK are good and of those cats that survive the perioperative period 85% no longer require insulin. Reasonable → response to cobalt irradiation have been reported. Medical management of acromegaly with somatostatin analogues has been ineffective.

Box 2 – Clinical signs of acromegaly in cats
- Weight gain despite poorly controlled DM.
- Change in body shape - increased body size, enlarged abdomen and head, prognathia
- Arthropathies
- Organomegaly
- Heart – murmur, cardiac hypertrophy and CHF.
- Liver, kidney, spleen
- Tongue – stridor and upper airway obstruction.

Pancreatitis
A number of surveys in dogs and cats have shown high rates of pancreatic changes in patients with diabetes, how closely associated these diseases are and the effect that pancreatitis has on diabetic stability is unclear and likely varies from individual to individual. Whether pancreatitis leads to diabetes or vice versa is also unclear (Davidson 2015).
In dogs, in particular, lipid dyschrasias associated with poorly controlled diabetes may be an important initiating factor. Risks of pancreatitis are cumulative and episodes of hypotension and hypovolaemia associated with DKA will also increase risks as well as the tendency for poorly controlled diabetics to scavenge. Necropsy findings indicate 35% of diabetic dogs have evidence of pancreatitis; this is historically associated with poor diabetic control suggesting that pancreatitis in dogs is a more significant comorbidity than it is in cats.
Many cats with diabetes have elevated pancreatic-specific lipase associated with chronic pancreatitis. Post mortem studies indicate around ⅔^{rds} of all cats have evidence of pancreatitis. It is unclear whether DM can induce pancreatitis or indeed with pancreatitis can induce DM.

Recent information suggests that the likelihood of a cat going into remission is not affected by the presence of pancreatitis indicating that for some cats, at least, pancreatitis does not necessarily make diabetic control more difficult.
Zini *et al* (2015) looked at criteria that would support pancreatitis in 30 newly diagnosed cats that suggested between 30 (fPLi or ultrasound) and 50% of cats (DGGR-lipase) had subclinical pancreatitis at diagnosis and that over the subsequent 6 months another 17-30% had positive results however only 1/30 cats showed compatible clinical signs and remission rates, as previously did not affect remission rates BUT lower fPLi at 2 months was associated with remission (fPLi ≤ 2.7µg/L predicting remission). In cats or dogs with positive pancreatic-specific lipase tests, there may be value in determining the level of systemic markers of inflammation (acute phase proteins) to try and estimate the effect that the pancreatitis may be having on diabetic control.

Hyperadrenocorticism
Approximately 5% of dogs with DM are also have HAC. However the diagnosis of HAC in diabetic dogs is fraught with difficulty as the metabolic consequences of diabetes tend to induce a stress-hypercortisolaemia and adrenomegaly leading to abnormal findings on both ACTH stimulation and dexamethasone tests as well as making ultrasound diagnosis challenging unless there is an adrenal mass.
Ideally the diabetes should be controlled to lower the metabolic stress and allow interpretation of adrenal function tests however this is challenging if the patient indeed has HAC due to increased insulin resistance associated with hypercortisolaemia. Using high doses of insulin risks hypoglycaemic crisis as cortisol production in HAC is not constant.
Management of HAC and DM is complicated and requires a dedicated client. Currently twice daily trilostane and insulin is the treatment of choice but ablating the adrenal glands with mitotane and managing an Addisonian diabetic has been used in some patients. If trilostane therapy is initiated rapid reduction in insulin requirements may occur. Trialling trilostane as a way of making a diagnosis is potentially risky as in non-HAC patients the high levels of cortisol are required to manage the metabolic stresses of poorly controlled DM. Faced with this situation advanced imaging is a better option. MRI is more definitive than CT but appropriate CT protocols have high sensitivity for pituitary macroadenoma at significantly lower cost and anaesthetic time.
HAC is a relatively rare endocrinopathy in cats with around 80% of HAC cases developing DM. Signs that suggest coexistence of these disease include seborrhoeic unkempt hair, skin thinning and fragility, alopecia, weakness and abdominal enlargement. Currently dexamethasone suppression testing (NB require 0.1mg/kg dexamethasone) carried out after initial attempts at stabilisation appears a reasonably sensitive and specific test and does not seem markedly affected by the degree of diabetic control that has been achieved at the time of testing.

Diabetic nephropathy
Between 17 and 63% of diabetic cats have evidence of CKD, what is unclear is whether this is comorbidities in an elder population or cause and effect. However, around 13% of newly diagnosed cases develop evidence of CKD in the first 6 months of management but in the absence of biopsy evidence, it is unclear whether this represents unmasking or progression of pre-exisiting disease. Post mortem studies of diabetic cats with age-matched controls do show differences but these are not statistically significant suggesting that if diabetic nephropathy does occur in cats it is of limited importance. Proteinuria is however, significantly more common in diabetic cats compared to healthy and sick controls – 75% vs. 18% vs. 34% but these cats were non-azotaemic and longitudinal follow-up not available. In dogs there is even less evidence regarding the existence and importance of diabetic nephropathy.
Regardless of this, diabetic patients with significant proteinuria (UPCR >1) should be treated with ACE inhibitor or ACE receptor inhibitor therapy.

Diabetic neuropathy
Diabetic neuropathy is significantly more common in cats than dogs characterised by distal segmental demyelination and remyelination as well as axonal degeneration and regeneration. In dogs it is primarily associated with chronic (>5 years) of poor diabetic control and seen as weakness, knuckling, abnormal gait, muscle atrophy, depressed limb reflexes and deficient postural reactions. There is no specific treatment apart form improving diabetic control that serves to minimise the metabolic consequences of diabetes.

Neuropathies in cats often appear earlier and typically as a plantigrade hind limb stance they are the most common diabetic complication in cats. Electron microscopy studies have shown that 90% of diabetic cats have peripheral nerve changes although <10% shown clinical evidence of neuropathy. Typically cats show hind limb weakness, inability to jump, ataxia and muscle atrophy; these changes may progress to include the forelimbs. Histologically changes are similar to those in man involving Schwann cells and axon damage to myelinated fibres. More rarely spinal pain syndromes are reported. Improving management of the diabetes will often result in substantial resolution of signs although electrophysiological abnormalities may persist. The value of other adjunctive treatments such as omega 3 fatty acids, L-carnitine and anti-oxidants is unclear.

Urinary tract infections

Urinary tract infections are common in diabetes and periodic urine culture is advised particularly in females or where there has been a history of previous infection. Infection is often silent and usually associated with glycosuria providing a medium for bacterial growth combine with urine being dilute. Clearly the best way to manage this issue is improving glycaemic control. Whether all urinary infections, if they are confined to the bladder and not associated with significant inflammation, lead to diabetic instability is unclear. However, the risk of ascending infection causing pyelonephritis should be borne in mind.

Conclusions

It is unknown how many diabetic dogs and cats have comorbidities that impact on their diabetic control, in a recent survey of 215 cats (Schaefer *et* al 2016), thirty-six of 202 (17.8%) cats had IGF-1 concentrations >1000 ng/ml. Serum fPLI, and TT4 concentrations and UCCR were increased in 86/196 (43.9%), 9/201 (4.5%) and 18/117 cats (15.3%), respectively. This would suggest in cats that around 20-30% of cats with diabetes are likely to have potentially significant comorbidities taking in to account the fact that a clear diagnosis was not established and the significance of raised fPLi on diabetic control. The figures in dogs show lower levels of comorbidity but when these occur such as HAC or pancreatitis they more profoundly affect diabetic control. A study of 221 dogs with diabetes mellitus by Hess *et al* (2000) showed 34 (21%) had a positive urine culture Escherichia coli was the most commonly isolated organism. Thirty-six (16%) dogs had dermatitis or otitis.. Acute pancreatitis was diagnosed in 28 (13%) dogs. Eleven (5%) dogs had tumours for which a histologic diagnosis was obtained. Eight (4%) dogs were hypothyroid. They report a relatively high percentage of dogs with HAC (23%) but this was primarily based on abnormal adrenocortical function testing that can be significantly affected by the metabolic stress of diabetes hence results need to be interpreted with care.

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