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Feline diabetes mellitus: background

Eric Zini

Epidemiology

Genetics

A breed predisposition for diabetes mellitus (DM) is demonstrated in cats and supports the hypothesis of a genetic component in the pathogenesis of the disease. In particular, in Burmese cats one in 50 develops the disease whereas in domestic cats the frequency is only one in 200. The predisposition in Burmese is not sex linked or dominant (Henson *et al.* 2006). Other breeds at increased risk of developing DM are Russian Blue, Norwegian Forest cat, and Abyssinian.

Obesity

Obesity in cats is generally defined as a 30% excess of body weight above normal; overweight animals are 10% to 15% above normal. In practice it is often preferable to use a body condition score (BCS) system to classify body condition and define overweight and obesity in cats. The prevalence of overweight cats, evaluated with BCS systems, is estimated to vary between 6% and 52%. Increased body weight predisposes cats to the development of insulin resistance and DM (Zoran *et al.* 2010).

Neutering

Neutering induces changes in basal metabolism and is one of the major risk factors for feline obesity. Both male and female cats increase their food intake and body fat mass following neutering. Alterations in sex hormones influence brain centers important for the control of food intake and metabolic rate and may result in increased energy intake and positive energy balance (Kanchuk *et al.* 2003). It has been demonstrated that gonadectomy removes the estrogenic inhibition of eating in female rodents and that these changes are reversed by estradiol treatment. A similar mechanism might explain obesity in neutered cats.

Pathogenesis of DM in cats

Insulin resistance

Inflammatory conditions may be an independent risk factor for insulin resistance and DM in cats. Burmese cats with chronic or recurring periodontal disease have impaired glycemic control and are more prone to develop diabetes. In obese cats, insulin sensitivity is typically decreased by more than 50% compared to healthy lean animals. In fact, each kilogram of weight gain reduces insulin sensitivity and glucose effectiveness in cats by 30% (Hoenig *et al.* 2007). Insulin resistance in diabetic and non-diabetic cats can therefore be reversed by reducing body weight. Interestingly, obese male cats have lower innate insulin sensitivity and higher basal insulin concentrations; this may therefore be one factor explaining why obese male cats are more prone to DM than obese females.

Glucotoxicity and lipotoxicity

In healthy cats, 10-day infusion of glucose or lipids were administered to mimic the milieu of DM. Severe β-cell dysfunction was rapidly induced by sustained hyperglycemia, resulting in β-cell exhaustion and decreased insulin gene expression (Zini *et al.* 2009). Furthermore, hyperglycemia caused β-cell loss due to apoptosis that was not compensated by increased β-cell proliferation. In contrast to the detrimental effects of sustained hyperglycemia, hyperlipidemia did not affect basal insulin levels or glucose-stimulated insulin secretion in healthy cats. Conflicting results have been described with regard to the effects of excess lipids on insulin secretion. Studies in rats and humans reported increased, decreased or unchanged β-cell function. Hence, to date, glucotoxicity might have a primary role during the progression of DM in cats.

Amyloid deposition

More than 80% of diabetic cats appear to have pancreatic amyloid deposition (Figure 1). Depending on the extent of amyloidosis in diabetic cats, this seems to be associated with an approximately 50% loss of β-cells mass (Ma *et al.* 1998). β-cell vacuolar degeneration, chronic

pancreatitis and a reduced number of islets or β-cells are other common histological findings in diabetic cat. However, not all cats with amyloid deposits develop diabetes and amyloid deposits are also present in non-diabetic cats. In agreement with these findings, the mean amyloid-positive cross-sectional area in the pancreatic samples of diabetic cats did not differ from matched control cats in a recent investigation (Zini *et al.* 2016). Deposition of amyloid is commonly believed to occur only in the extracellular compartment (i.e., within the islets but outside the β-cells). Based on a recent investigation in diabetic cats, aggregates of amylin fibrils or oligomers can be identified also within β-cells (Figure 2). This observation may point towards a role of intracellular deposition in the pathogenesis of β-cell failure (Zini *et al.* 2017).

Inflammation and insulin resistance

Inflammation, particularly in adipose tissue, has been causally linked to diet- and obesity-related insulin resistance and to the development of type 2 DM in several human and rodent studies.

Adipokines and adipocytokines

Similar to humans, secretion of adipokines like leptin and adiponectin from adipose tissue has been shown in cats (Radin *et al.* 2009). Higher circulating concentrations of leptin positively correlate with insulin resistance; it was claimed that this may even occur independent of changes in BCS and fat mass. The association between increased leptin levels and neutering is most probably related to the increase in fat mass gained post-neutering. However, a causal inter-relationship between leptin, insulin resistance and diabetes has not been demonstrated in cats.

In cats, adiponectin is produced and secreted exclusively by mature adipocytes; its gene expression is significantly higher in visceral than other adipose depots. Recent reports showed that the high molecular weight (HMW) multimers of adiponectin account for about 80% of total adiponectin in cats. HMW multimers are more closely associated with insulin sensitivity and body fat mass than total adiponectin. Plasma adiponectin concentrations negatively correlate with increases in fat mass, and circulating levels of adiponectin are significantly lower in obese than in normal-weight cats. Further, it seems that total adiponectin levels are lower in obese neutered male than in female cats, although this gender difference may not be directly attributable to sex hormones levels. The role of adiponectin as anti-inflammatory adipokine has not been investigated in cats.

Several studies in cats have shown that TNF-α expression in adipose tissue and in skeletal muscle is increased in obese cats (Hoenig *et al.* 2006). However, there is a lack of published data regarding the circulation patterns of adipose-derived TNF-α and other cytokines in cats, probably due to the unavailability of reliable assays. Gene expression of insulin signaling-related genes is decreased in insulin sensitive tissues of obese cats. For instance, obese cats have decreased GLUT4 expression in muscle and fat, and IRS-2 mRNA levels are lower in skeletal muscle and liver.

Inflammation and nutrient metabolism

Subacute inflammation was induced by lipopolysaccharide (LPS) infusion in healthy cats, in the absence of obesity (Osto *et al.* 2011). This manipulation was sufficient to cause a transient insulin resistance state at the whole-body level, and a long-lasting peripheral and tissue-specific insulin resistance in cats; both effects were observed without significant effects on pancreatic β-cell function. LPS infusion also led to an increase of circulating and tissue markers of inflammation in cats. Further, mRNA and protein analysis revealed that expression of key genes involved in glucose, lipid and insulin metabolism were altered in a manner consistent with a tissue-specific reduction in insulin sensitivity. Major changes were observed in adipose tissue and in particular in the subcutaneous fat depot. This included a reduced adipocyte size due to increased hormone sensitive lipase activity, decreased high density lipoprotein cholesterol levels and increased triglyceride levels in plasma and liver; all changes pointed to severe dyslipidemia. The observation that adipocyte size in both fat depots of LPS-infused cats was significantly decreased and that subcutaneous compared to visceral fat was found to exhibit a much higher expression of pro-inflammatory factors was particularly noteworthy. In fact, recent findings showed that in addition to adipose mass and distribution, mean fat cell size is associated with metabolic complications such as insulin resistance and adipose tissue inflammation in humans. Further, it has been

demonstrated that an increased proportion of small adipose cells in human subcutaneous adipose tissue is associated with inflammation, independently of body mass index and insulin resistance. Whether such factors play a role in cats is currently unknown.

Inflammation and β-cell function

Interestingly, both experimental hyperglycemia and hyperlipidemia induced a systemic inflammation in healthy cats which resembled that observed in human T2DM. However, in contrast to the findings in humans, local inflammatory reactions in the islets were not observed after the hyperglycemic or hyperlipidemic clamps in cats. Hence, although hyperglycemia (but not hypertriglyceridemia) has detrimental effects on the endocrine pancreas, these effects did not seem to depend on the activation of local inflammatory responses, at least during 10-day infusions of glucose or lipids, respectively. It was also demonstrated that β-cell function was impaired during the initial days of endotoxin infusion but that this effect was no longer detectable by day 10 of the infusion.

Recently, it was assessed whether diabetic cats have pathological evidence of islet inflammation or pancreatitis and found that the average counts of neutrophils, T- and B-lymphocytes in the islets did not differ between diabetic and healthy cats although the presence of lymphocytes in general tended to be more frequent in diabetic than control cats (Zini *et al.* 2016). In addition, a subset of diabetic cats showed lymphocytic infiltration of the islets that might contribute to β-cell loss. These results confirm previous observations that loss of β-cells occurs in diabetic cats and suggest that increased necrosis and fibrosis of the exocrine tissue may be associated with pancreatitis in at least some diabetic cats.

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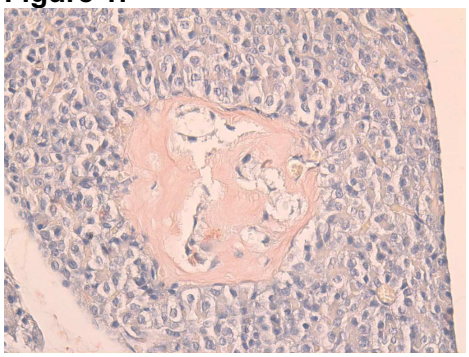
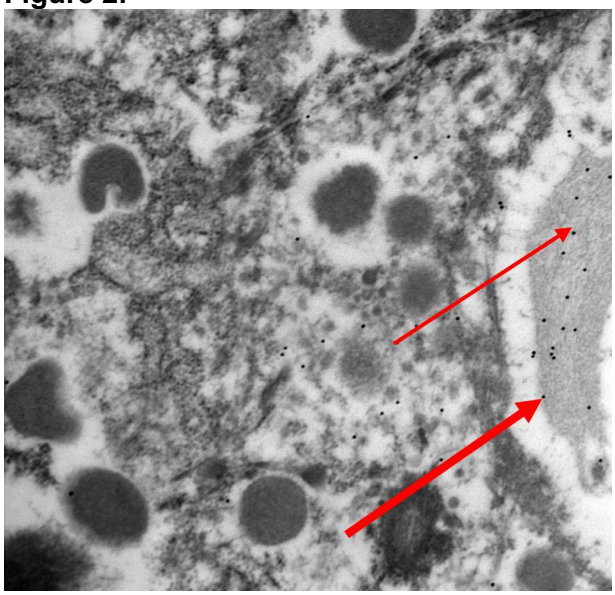
Figure 1.



Pancreatic islet of a diabetic cat with large deposits of amyloid. Light microscopy, Congo red staining.

Figure 2.



Amylin aggregates in the cytoplasm of a β-cell in a diabetic cat; the red arrows show labeling of amorphous material with amylin antibodies (black dots). Electron microscopy, amylin-immunogold.