PATHOGENESIS OF FELINE DIABETES MELLITUS

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Classification

Type 1 diabetes is uncommon in cats based on histological studies and absence of islet cell antibodies

Type 2 diabetes is the most common form of diabetes in cats, based on islet histology, risk factors, and clinical behavior of the disease. Type 2 diabetes is characterised by inadequate insulin secretion and impaired insulin action (insulin resistance).

A substantial minority of diabetic cats have other specific types of diabetes and include diseases causing insulin resistance, and those resulting from non-specific destruction of pancreatic tissue. These include pancreatic adenocarcinoma, pancreatitis, acromegaly, and hyperadrenocorticism. Iatrogenic administration of megestrol acetate or long-acting steroids is associated with diabetes in cats.

Type 2 diabetes

In Type 2 diabetes insulin resistance is associated with genotype, obesity, physical inactivity, and some drugs.

Insulin resistance and obesity

Obesity causes insulin resistance and is a risk factor for the development of diabetes in cats, although not all cats with type 2 diabetes are overweight..

Genetics of type 2 diabetes

Strong evidence for a genetic basis for the disease comes from the higher incidence of diabetes within some families of cats and ethnic groups of people. In humans, multiple genes are likely to be involved in predisposition to type 2 diabetes; genes controlling insulin secretion and action, and genes influencing factors such as propensity to obesity.

Breed is also a risk factor in cats. The incidence of diabetes is over-represented in Burmese cats in Australia, New Zealand, and the United Kingdom. The frequency of diabetes in Burmese cats is approximately 4 times higher than that of Domestic cats in Australia.

Age

Increasing age is also a risk factor for type 2 diabetes. Most cats are older than 8 years of age when diagnosed, with a peak incidence between 10 and 13 years of age. Although 1 in 50 Burmese cats have diabetes, this increases to 1 in 10 for Burmese cats 8 years or older.

Obesity and physical inactivity

Environmental or lifestyle factors shown to be important in humans and probably in cats, include obesity, physical inactivity, dietary factors, and urban rather than rural residence. Exclusively indoor cats are usually less active than outdoor cats that hunt and defend territory. In humans and rats, exercise increases insulin sensitivity. Lack of exercise impairs insulin action, and adds to the underlying level of genetically-determined insulin resistance.

Obesity associated with insulin resistance is an important risk factor in the development of type 2 diabetes in humans and cats. In a study where cats were allowed free-access to a highly palatable energy dense diet over 10 months and increased their bodyweight by 44%, their insulin sensitivity decreased by more than half. Following weight gain 25% of these cats had insulin sensitivity values within the range reported for diabetic cats.

Diet and type 2 diabetes

Overfeeding of highly palatable, calorie-dense food in cats with reduced physical activity, likely contributes to obesity, and hence diabetes. Recent evidence in cats suggests that a high carbohydrate diet increases the demand for insulin secretion when compared to a low carbohydrate, high protein diet. In susceptible cats, this long-term demand for increased insulin secretion may lead to beta cell apoptosis and a decline is insulin secretory capacity, precipitating impaired glucose tolerance and diabetes, as hypothesized by the Carnivore Connection Theory. *Ad libitum* feeding of cats is not recommended except in the few cats which self-regulate food intake and maintain an ideal body condition.

Amyloid

Many, but not all cats and humans with diabetes, have amyloid deposition replacing islets cells. Amyloid deposition does not appear to be an essential component of type 2 diabetes in either species, but is associated with beta cell loss and failure of insulin secretion.

Glucose and lipid toxicity

Once persistent hyperglycaemia occurs, insulin secretion is reduced through a phenomenon termed glucose toxicity. There is evidence that initially, suppression of insulin secretion is functional and reversible. With hyperglycaemia of longer than 2 weeks duration, histological abnormalities are evident, including glycogen deposition and cell death. The severity of the glucose toxicity effect is dependent on the degree of hyperglyceamia and the duration.

Increased fatty acids produce a similar effect to glucose toxicity, called lipotoxicity.

The clinical implications of glucose and lipid toxicity are very important. It is vital that hyperglycemia is reduced as soon as possible in diabetic cats, if beta cell function is to be preserved. Most cats will undergo remission of their diabetes, if the effects of glucose toxicity are minimised.

Insulin resistance and chronic hyperglycemia

Chronically elevated blood glucose also causes insulin resistance. This has implications for therapy, because once glucose concentrations are decreased with treatment, insulin sensitivity may improve.

Diabetic remission or transient diabetes

Diabetic remission occurs in up to 90% of newly diagnosed cats if treated appropriately. Remission occurs most commonly after 1 to 4 months of insulin therapy, and is more likely if glycaemic control is optimum, so beta cells can recover from glucose toxicity. Therefore, insulin therapy is recommended as the initial therapy to maximise control of blood glucose and increase the probability of remission.

Clinical Signs and Diagnosis

There are no internationally agreed criteria for diagnosis of diabetes mellitus in cats. Clinical signs such as polydypsia/polyuria, weight loss, or polyphagia are non-specific, and diagnosis cannot be confirmed on clinical examination. Diagnosis in cats is often complicated by stress hyperglycaemia, which in sick non-diabetic cats may lead to glycosuria or blood glucose levels in excess of 360 mg/dL (20 mmol/L). Blood glucose in non-diabetic unstressed client-owned cats is usually less than 171 mg/dL (9.5 mmol/L), however struggling can transient hyperglycemia as high as 288 mg/dL (16 mmol/L) in normal cats. Blood glucose should be measured several hours after the first sample to confirm persistent hyperglycemia. Signs of diabetes occur once blood glucose concentration exceeds the renal threshold, which is approximately 250-288 mg/dL (14-16 mmol/L) for normal cats.

Fructosamine may be useful in assisting diagnosis, especially when typical clinical signs of diabetes are not present. However, false positive and negative results can occur. A fructosamine level of greater than 400 µmol/L in a cat strongly supports a diagnosis of diabetes.

Measurement of water intake is inexpensive and useful for confirming polydypsia once blood glucose is above the renal threshold. In normal cats, total water intake including water in food ranges from 60 to 100 mL/kg/24h, but average water drunk is approximately 20 mL/kg or less.

If there is doubt whether the hyperglycemia 270 mg/dL (15 mmol/L) is transient and associated with stress or is from diabetes, in sick cats it is prudent to begin insulin therapy and monitor glucose concentrations carefully for the next few days. Reducing glucose concentrations with exogenous insulin reduces the suppressive effect of glucose toxicity and makes recovery of beta cells more likely. Therapy for the underlying disease can then be instituted and glucose concentrations monitored to adjust insulin dose.

Ketoacidosis

Ketoacidosis occurs in approximately 12 – 37% of diabetic cats at the time of diagnosis, and a smaller percent are ketotic without acidosis. Ketoacidosis results in depression, vomiting and anorexia. Ketoacidosis can be precipitated by concomitant disease, especially infection. However, once cats become markedly insulinopaenic, even previously normal cats progress to ketosis within 10 – 30 days. In experimentally induced diabetes, ketonaemia occurred on average 5 days before ketonuria was detected using a urine test strip. Although ketotic cats usually have low insulin concentrations, with appropriate therapy to overcome glucose and lipotoxicity, some beta cell function may return, and many of these cats achieve remission.

Principles of therapy

Therapy for diabetes should be instituted as soon as possible after diagnosis and administration of insulin and dietary modification are the principal therapies. The main aim of therapy is to achieve exemplary glycaemic control to facilitate remission. In cats in which remission is not possible, resolution of clinical signs and avoidance of clinical hypoglycaemia are the goals. Oral hypoglycaemic drugs are not recommended unless blood glucose is persistently elevated but in the prediabetic range (< 10 mmol/; 180 mg/dL). A recent study has shown that if good glycaemic control is achieved early in newly diagnosed diabetic cats, very high remission rates occur within 8 weeks of treatment. Good glycaemic control reverses the glucose toxicity suppressing beta cells, and maximises the chance of preserving beta cell function and achieving diabetic remission.

Summary

Understanding the pathogenesis of feline diabetes is important for good patient management, and may help to decrease the incidence of diabetes.