Pathogenesis of Feline Diabetes

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KEYWORDS

• Feline • Diabetes mellitus • Type 2 diabetes • Pathogenesis

KEY POINTS

- Diabetes is essentially a disease of insulin secretory failure caused by damage to pancreatic islet β cells.
- Diabetes in cats is most commonly type 2, which is caused by β-cell failure in the presence of insulin resistance caused by obesity.
- The mechanisms of β-cell failure are still debated, but intracellular amyloid oligomers are a likely contributor in early stages, and glucose toxicity contributes to further β-cell damage and maintenance of the diabetic state.
- Other causes of β-cell failure include widespread damage to the pancreas by pancreatitis, and diseases that increase insulin resistance such as acromegaly.
- Diabetes is a disease of insulin deficiency.
- Insulin requirement can be increased by obesity, acromegaly, inflammation, and concurrent endocrine disease.
- Insulin secretion can be decreased by damage to pancreatic β cells by inflammation, glucose toxicity, reactive oxygen species, toxic intracellular oligomers, or mechanisms as yet unknown.

INTRODUCTION

Diabetes mellitus (diabetes) is defined as persistent hyperglycemia caused by a relative or absolute insulin deficiency. Insulin is exclusively produced by the β cells of the islets of Langerhans in the pancreas, and insulin deficiency occurs when β cells are destroyed or their function is impaired. The mechanisms involved in causing loss of β-cell function are the basis for the classification of diabetes. The mechanisms underlying β-cell damage might also create therapeutic targets to prevent the onset of diabetes or specific treatment of the underlying disease process.

At present there is no consensus in the veterinary literature on what blood glucose concentration should be classed as diabetic. Typically diabetes is diagnosed when blood glucose concentration is above the renal threshold, causing obligatory water loss and hence the signs of polyuria and polydipsia. These signs are associated with

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a blood glucose concentration of 14 to 16 mmol/L (234–288 mg/dL) or higher.[1] Various cutpoints have been used in the veterinary literature, and 10 mmol/L (180 mg/dL) was proposed by Crenshaw and Peterson.[2] In human patients, however, the cutoff blood glucose concentration for diabetes mellitus has been lowered consistently over time as more information has become available on the adverse effects of mild hyperglycemia, including microvascular damage and retinopathy. At present, 7.1 mmol/L or 126 mg/dL is used.[3] Cats notably have fasting glucose concentrations similar to those of humans.[4] Recent research in client-owned cats suggest that the cutpoint for normal fasting glucose concentration is 6.3 mmol/L in healthy, nonobese cats 8 years of age or older, and cats with persistent glucose concentrations above this value but below diabetic concentrations should be considered as having impaired fasting glucose.[5] Humans with impaired fasting glucose or impaired glucose tolerance based on increased 2-hour glucose concentrations in a glucose tolerance test are considered prediabetic and at greatly increased risk of developing diabetes. A recent study of diabetic cats in remission found that fasting glucose concentrations greater than 6.5 mmol/L (117 mg/dL) or glucose concentration greater than 6.5 mmol/L (117 mg/dL) at 4 hours after a glucose challenge (1 g/kg) were predictive of relapse, suggesting that cats with glucose concentrations greater than 6.5 mmol/L should also be considered prediabetic.[5] In humans, approximately 50% of patients with diabetes are undiagnosed, and there are 2 to 4 times more patients considered prediabetic than diabetic.[3] It is likely that there are also many undiagnosed diabetic and prediabetic cats.

In humans, diabetes is classified based on the pathogenesis of β-cell failure as type 1, type 2, gestational diabetes, and other specific types of diabetes.[6] Type 1 diabetes is caused by autoimmune damage to pancreatic β cells. Type 2 diabetes is characterized by insulin resistance with concomitant β-cell failure, which in humans is often relative rather than absolute failure of insulin secretion. Type 2 diabetes occurs when β cells fail to secrete adequate insulin, although there is no consensus about the leading mechanism(s) of β-cell damage. Typically type 2 diabetes occurs when insulin requirements are increased by a chronic fuel surfeit and insulin resistance.[7] Insulin sensitivity/resistance has a genetic predisposition,[8] but the most common acquired insulin resistance in type 2 diabetes is obesity associated. In type 2 diabetes insulin secretion is defective, and is insufficient to compensate for the insulin resistance. Gestational diabetes is defined as diabetes that is first diagnosed during pregnancy.[9] If diabetes persists after the end of pregnancy, it is reclassified as one of the other types. The classification "other specific types of diabetes" includes all the other causes of diabetes.[6] Broadly these include diseases that damage the whole pancreas (such as pancreatitis, pancreatic carcinoma, and pancreatectomy), toxic causes of β-cell damage (such as by the antineoplastic drug streptozotocin or rare drug reactions such as to the thiazide diuretics, glucocorticoids, and thyroid hormone), genetic causes of diabetes (resulting in β-cell failure or insulin resistance, such as various rare single-gene causes of diabetes and leprechaunism), and diabetes types associated with other endocrine diseases (such as hyperadrenocorticism, acromegaly, and glucagonoma).

In cats, diabetes that is analogous or similar to several human diabetes types has been recognized. Most commonly, feline diabetes is of a type similar to type 2 diabetes.[10] Cats also exhibit several types of diabetes that under the human classification system would be classified as other specific types, including diabetes associated with acromegaly,[11] hyperadrenocorticism, and pancreatic carcinoma.[12] Although many diabetic cats have histologic evidence of pancreatitis, in some cats it is not clear whether the diabetes is the cause or consequence of chronic pancreatitis.[12,13] Some diabetic cats, however, do have classic signs and biochemical evidence of acute pancreatitis at the time of onset of diabetes, and may later achieve remission

at a time when clinical and biochemical signs of pancreatitis have resolved. Clinical and histologic findings consistent with type 1 diabetes was reported in a 5-month-old kitten,[14] and recent research has demonstrated T-cell lymphocytes within pancreatic islets of diabetic cats, suggesting that autoimmune damage and, therefore, type 1 diabetes might occur in cats,[13] although it appears to be very rare.

PATHOGENESIS OF TYPE 2 DIABETES IN CATS

Human type 2 diabetes has a complex etiology and is caused by a combination of genetic factors and environmental interactions, and there is an increased risk with aging. There is strong evidence that the same factors are also important in cats.

The susceptibility to type 2 diabetes in human beings, monkeys, and rodents is inherited, and there are preliminary data supporting a genetic influence in cats.[12] Diabetes is most common in domestic long-haired and short-haired cats. Burmese cats are overrepresented, and many other pure breeds are underrepresented, in comparison with the incidence in domestic cats. The Burmese breed is overrepresented in Australia, New Zealand,[15,16] and the United Kingdom.[17] The frequency of diabetes in the Burmese breed is approximately 4 times the rate in domestic cats in Australia, with 1 in 50 Burmese affected compared with less than 1 in 200 domestic cats.[18] In some Burmese families, more than 10% of the offspring are affected.[18] The genetic factors predisposing cats to diabetes are unknown.

In human patients, a family history of type 2 diabetes is an important risk factor, increasing the risk by 3.5 and 6 times if one or both parents are diabetic, respectively.[19] There is a high concordance rate of diabetes in identical twins, and to a lesser degree also in nonidentical twins. In one study of identical twins the concordance rate was 58%, in contrast to an expected prevalence of 10%.[20] This high concordance rate is highly suggestive of a genetic determination. However, the fact that concordance rates do not reach 100% in identical twins, which share 100% of their genes, means that genetic factors are not solely responsible for the development of diabetes.

Although the genetics of type 2 diabetes are far from being well established, there are interesting trends emerging. It has been discovered that most of the genetic markers associated with increased risk for the metabolic syndrome, a prediabetic syndrome in humans, are located within genes known to be associated with lipid metabolism.[8] Studies in humans examining genetic contributors to obesity, the major preventable risk factor for type 2 diabetes, have found more than 30 associated genes, with many of these involved in neural function.[21] This finding supports the hypothesis that hypothalamic or other neural function underlies the development of obesity.[22] Other genes associated with type 2 diabetes code for proteins that are involved in insulin sensitivity, insulin signaling, and the regulation of gene transcription.[21]

In a recent study in Burmese cats, lean Burmese demonstrated gene expression patterns similar to those of as age-matched and gender-matched obese domestic cats for the majority of the genes examined, and the pattern of gene expression suggested possible aberrations in lipogenesis.[23] Moreover, lean Burmese displayed an approximately 3- to 4-fold increase in the percentage of very-low-density cholesterol fraction, which was double that of obese domestic cats, indicating an increased degree of lipid dysregulation, especially in relation to triglycerides. The findings of this study suggest that Burmese cats have a genetic propensity for dysregulation in lipid metabolism, which may predispose them to diabetes in their senior years.[23]

The key to understanding the pathogenesis of type 2 diabetes is to recognize that in normal individuals β cells are responsive to the need for insulin secretion, and will undergo hypertrophy and hyperplasia to meet increased insulin needs.[24] Insulin needs

change largely as a result of changes in insulin sensitivity. Insulin sensitivity is defined as the effectiveness of a given concentration of insulin to decrease blood glucose. If insulin sensitivity is decreased (ie, if insulin resistance occurs), more insulin is needed to maintain glucose concentrations below the set point for insulin secretion. Type 2 diabetes occurs when insulin sensitivity is decreased and compensatory insulin secretion fails in association with β-cell failure.

Decreased Insulin Sensitivity

Insulin sensitivity varies widely even in normal cats, but is lower in males and is decreased in obesity.[25] In human beings, insulin sensitivity is also decreased in various disease states including inflammatory disease,[26] polycystic ovary syndrome,[27] hyperadrenocorticism,[28] and pheochromocytoma,[29,30] in response to drugs such as glucocorticoids and atypical antipsychotic agents,[31,32] and during pregnancy.[9] In both cats and humans, obesity is the leading acquired cause of insulin resistance. For example, weight gain of 44% over 10 months in cats resulted in a 50% decrease in insulin sensitivity.[25] Obesity causes insulin resistance through a variety of mechanisms, including changes in adipose-secreted hormones, and through systemic inflammatory mediators.[33,34] Acromegaly appears to be an underdiagnosed cause of insulin resistance in diabetic cats[11] (see the article elsewhere in this issue on hypersomatotropism, acromegaly, and hyperadrenocorticism and feline diabetes mellitus.), whereas hyperadrenocorticism is a rare cause of feline diabetes[35] (see article by Niessen SJM and collegues elsewhere in this issue).

Hormones secreted by adipose tissue (adipokines) were first discovered around 20 years ago, and since then more than 100 such hormones have been discovered. One adipokine of particular importance to diabetes is adiponectin, a hormone that has effects on the liver, skeletal muscle, the pancreatic islets, and adipose tissue itself.[36] Unlike other adipokines, adiponectin concentrations are decreased with increasing obesity. Because adiponectin increases insulin sensitivity, the decreased concentrations that occur with obesity are associated with insulin resistance. Adiponectin is present in circulation as multimers composed of varying numbers of trimers.[37] Low molecular weight trimers and hexamers (collectively called low molecular weight adiponectin) have less biological activity on glucose homeostasis than high molecular weight multimers composed of 12, 18, or more adiponectin monomers.[38] In cats, adiponectin has been shown to be associated with diet[39] and obesity,[40] but studies linking it with insulin sensitivity and diabetes are currently lacking. Leptin has also been examined in cats. Leptin concentrations are increased in obesity,[40–42] and are independently associated with decreased insulin sensitivity,[41] and therefore may be associated with the pathogenesis of diabetes in cats.

Other adipokines are secreted by adipose tissue in increasing concentrations in the presence of obesity.[33] Many of these are inflammatory mediators, including interleukins and tumor necrosis factor.[34,43] These hormones decrease the intracellular effects of insulin by increasing phosphorylation of insulin receptor substrate, which mediates the effects of insulin after it binds to insulin receptors in muscle and adipose tissue.[43] By decreasing the effects of insulin, these proinflammatory adipokines are involved in decreasing insulin sensitivity.

Decreased Insulin Secretion

Insulin secretion is increased in response to decreased insulin sensitivity.[24] In normal individuals, insulin secretion increases as insulin sensitivity decreases, and the product of insulin secretion and insulin sensitivity (ie, insulin secretion multiplied by insulin sensitivity) stays constant.[44] However, compensation fails once β cells are

unable to further increase insulin production, or when more insulin-producing β cells cannot be produced by compensatory hypertrophy. In the past, β-cell "exhaustion" secondary to chronic hyperfunction has been invoked as a simplistic explanation of β-cell failure in insulin-resistant individuals. However, many individual insulin-resistant cats[10] and humans[45,46] compensate adequately for insulin resistance and do not progress to diabetes mellitus. Similarly, type 2 diabetes does not appear to occur at all in other species such as dogs, even though they do exhibit similar degrees of insulin resistance.[47] The concept of β-cell exhaustion lacks a mechanistic basis and fails to explain species differences in susceptibility to type 2 diabetes, which occurs in humans,[6] cats,[10] some nonhuman primates,[48] and laboratory rodents,[49] but not in dogs[10] or other species, regardless of the presence of obesity. Other endocrine cells do not exhibit exhaustion (eg, chronic stress does not lead to hypoadrenocorticism and chronic dehydration does not cause diabetes insipidus), so it seems improbable that an increased requirement for insulin secretion per se leads to β-cell failure.

Recent work in gestational diabetes in human beings has advanced the understanding of the development of diabetes mellitus in insulin-resistant states.[9] Pregnant women are insulin resistant, and some women develop diabetes during pregnancy but recover after giving birth.[50] These women are at increased risk for developing diabetes subsequently, and the relative prevalence of each of the categories of diabetes that these women subsequently develop is very similar to that in the wider population.[9] This fact suggests that insulin resistance itself does not cause diabetes, but rather that it highlights individuals with early stages of β-cell failure by increasing the demand for insulin. This increased demand cannot be met by the failing β cells. It seems likely that obesity and other insulin-resistant states act similarly to increase the need for insulin secretion by β cells, which cannot be met in individuals whose β cells are damaged by some other disease process. In fact, obesity increases the demand on β cells to produce insulin while processes associated with obesity simultaneously appear to damage β cells, reducing secretory capacity.

Theories about the cause of this failure of compensation have included damage to pancreatic islets by amyloid deposition and a variation of the amyloid hypothesis called the toxic oligomer hypothesis; toxicity by glucose, lipids, or both; reactive oxygen species; and inflammatory cytokines.

Amyloid is an accumulation of protein strands that have refolded from their normal, functional shape to form abnormal, nonfunctional, β-pleated sheets.[51] Protein in β-pleated sheet conformation is resistant to degradation by proteases, and tends to recruit more protein to transform into the altered conformation, so that more and more amyloid material accumulates.[51] Within pancreatic islets, the abnormal protein that forms amyloid has been identified as amylin (also called islet amyloid polypeptide), a hormone that is cosecreted with insulin and is secreted in disproportionately larger quantities in individuals with insulin resistance, which increases the amount of amylin available to contribute to amyloid accumulation within pancreatic islets.[51] Amyloid is almost universally present in individuals with type 2 diabetes (both humans and cats[51,52]). In an experimental model of induced diabetes in cats, islet amyloid was not evident before the induction of diabetes, but was present in all 4 glipizide-treated and in 1 of 4 insulin-treated cats 18 months after diabetes was induced by 50% pancreatectomy and 4 months of dexamethasone and growth hormone treatment.[53] Islet amyloid was an appealing potential cause of β-cell failure, especially because it explains the species differences in susceptibility to type 2 diabetes. The amino acid sequence of amylin in dogs is different from that in humans and cats, and does not form β-pleated sheets in dogs. However, the amyloid theory has largely been abandoned as a viable hypothesis for several reasons. First, the amyloid hypothesis fails

the test of dose-response; that is, the severity or likelihood of diabetes and the degree of impairment of insulin secretion are not related to the amount of amyloid present in islets. Second, many normal individuals have amyloid within the islets but have normal insulin secretion. Finally, the amyloid hypothesis seems implausible because all cells within pancreatic islets (α, β, and δ cells) are exposed to amyloid but only β-cell function is impaired, whereas glucagon production by α cells is increased in type 2 diabetes.[54,55]

The toxic oligomer hypothesis is similar to the amyloid hypothesis in that it is also based on toxicity of polymerized, misfolded amylin, but differs from the amyloid hypothesis because toxicity is attributed to intracellular amyloid fibril rather than the inert extracellular form.[56,57] Unlike amyloid, which is visible with light microscopy, intracellular amyloid fibrils are not visible at the microscopic level but trigger β-cell death through the misfolded protein response, which triggers programmed cell death (apoptosis) when misfolded protein is detected within the endoplasmic reticulum.[57,58] The toxic oligomer hypothesis helps explain why β cells are affected by amyloid toxicity whereas other islet cells are not, because only β cells produce amyloid, and so are the only cells that are exposed to the more toxic nanofibrils that form intracellularly.[58] It also accounts for why cats and humans, but not dogs, are susceptible to type 2 diabetes. However, more work is needed to clarify the role of amylin oligomers in the pathogenesis of type 2 diabetes, because there are still limitations with this hypothesis, including clarification of the oligomers involved and the importance of the role of toxic oligomers.[59] One important limitation is that amylin and insulin are cosecreted, so that individuals with insulin resistance and compensatory hyperinsulinemia also have high amylin secretion and should form toxic amylin oligomers. However, this does not occur for many individuals. Modifications of the theory are still needed to clarify the conditions under which amylin forms toxic intracellular oligomers.[59]

Glucose toxicity was initially proposed to occur at very high glucose concentrations (>15 mmol/L, 540 mg/dL) and to act as a secondary mechanism that would accelerate β-cell failure in individuals with some other cause of inadequate insulin secretion.[60] However, subsequent studies in rats found that glucose toxicity can cause impaired β-cell function at glucose concentrations that are only 1 mmol/L (18 mg/dL) higher than normal, suggesting that it acts much earlier in the pathogenesis of diabetes than had previously been thought. Chronic hyperglycemia and hyperlipidemia contribute to changes in the microenvironment in the endoplasmic reticulum, where proteins are assembled, modified, and folded. These changes in the endoplasmic reticulum can trigger β-cell death through the unfolded protein response, a mechanism that monitors the volume of proteins that have not folded and assembled properly and which can trigger apoptosis if the number of such proteins is too high. This mechanism is an important contributor to β-cell death in diabetes.[61] Cats are susceptible to glucose toxicity at high glucose concentrations,[62] and good control of blood glucose concentrations in diabetic cats can lead to remission of diabetes,[63] so glucose toxicity very likely plays an important role in the development or maintenance of inadequate insulin secretion in type 2 diabetes in cats. However, the initial development of abnormally high blood glucose concentrations implies that insulin secretion is already impaired before glucose toxicity can exist, meaning that glucose toxicity is an unlikely primary mechanism in the development of type 2 diabetes.

Damage to β cells by reactive oxygen species is proposed as a primary mechanism causing initiation of β-cell damage, thus triggering the development of impaired insulin secretion, and also as a mechanism to promote or maintain further β-cell death in individuals with existing diabetes.[64] Reactive oxygen species are generated when there is excess fuel (such as glucose or fatty acids) in the cell.[64,65] β Cells are particularly prone to this because intracellular glucose concentrations reflect plasma glucose

concentrations, allowing β cells to sense and respond to changes in plasma glucose.[64] Oxidation of intracellular glucose and fatty acids causes increased electrochemical gradients across the mitochondrial membrane, which can damage the cell by causing increased production of reactive oxygen species. Affected cells respond by producing uncoupling protein 2, which safely dissipates the increased electrochemical gradient, but at the expense of production of adenosine triphosphate (ATP). Because ATP production within β cells is the trigger for insulin secretion, production of uncoupling protein 2 has the effect of keeping the β cells alive, but still has the effect of decreasing insulin production.[65] However, this theory by itself does not explain why cats and humans, but not dogs, develop type 2 diabetes.

Inflammation triggered by autoimmunity has long been known to have a role in type 1 diabetes, but there is also evidence of inflammation in type 2 diabetes.[66] Pancreatic islets in humans with type 2 diabetes exhibit inflammatory cell infiltration, increased cytokine expression, and fibrosis, the hallmark of chronic inflammation.[66] Inflammation is triggered within pancreatic islets as well as systemically by adipose tissue. Adipose tissue (adipocytes themselves and macrophages that reside alongside adipocytes) can secrete many cytokines, and obesity is associated with systemic changes in inflammatory proteins including cytokines such as tumor necrosis factor and interleukins,[67] and acute phase proteins such as C-reactive protein, haptoglobin, and fibrinogen.[66] In addition, β cells themselves secrete cytokines, especially interleukin-1, which initiate an inflammatory cascade in response to nutrient overload.[66] Proinflammatory cytokines, whether secreted remotely or locally by β cells, affect β-cell function and can trigger apoptosis. Recent trials in humans suggest that this mechanism can be targeted to protect against the development of type 2 diabetes.[68] Studies of this group of mechanisms in cats have not been done.

In summary, none of the proposed mechanisms of β-cell failure, except amyloid oligomers, explains the difference in species susceptibility to type 2 diabetes, and this theory needs further refinement to explain individual differences in susceptibility of insulin-resistant individuals to type 2 diabetes.

PATHOGENESIS OF FELINE ACROMEGALY (HYPERSOMATOTROPISM)

Although obesity is the most common cause of insulin resistance that leads to increased insulin requirements and diabetes mellitus, other causes have been documented. One such is acromegaly, which is the result of increased secretion of growth hormone by a pituitary tumor.[11] Diabetes caused by acromegaly typically involves cats with extreme insulin resistance and, hence very high insulin dose requirements.[69] However, with increased surveillance for acromegaly, feline diabetic patients are being diagnosed that are not clinically insulin resistant based on insulin dose, and occasionally achieve remission without treatment for acromegaly (Stjin Niessen, personal communication, 2012). What is not currently understood is whether or how acromegaly (and other endocrine diseases that cause insulin resistance and are associated with other specific types of diabetes) contributes to β-cell failure. Acromegalic cats have evidence of β-cell hyperplasia and following successful tumor removal, some cats exhibit transient signs of hypoglycemia, which can be severe and life threatening (Hans Kooistra, personal communication, 2012). This subject is covered in more detail in the article elsewhere in this issue on hypersomatotropism, acromegaly, hyperadrenocorticism, and feline diabetes mellitus.

PATHOGENESIS OF PANCREATITIS-ASSOCIATED DIABETES

Pancreatitis causes diabetes by causing widespread inflammatory damage and fibrosis throughout the exocrine pancreas, which incidentally also destroys the

endocrine pancreas.[10] The difficulty of reliably diagnosing pancreatitis in cats is exacerbated by the limited research on this clinical entity,[70] but there are several features expected in cats with pancreatitis-associated diabetes. Pancreatitis in cats is strongly associated with inflammatory bowel disease and cholangiohepatitis.[71] These disorders are chronic inflammatory diseases that are expected to cause waxing and waning insulin resistance as well as very variable insulin requirements, intermittent loss of appetite and ketosis, and weight loss. The outcome is diabetic cats that are difficult to regulate well because of changing insulin requirements and periodic appearance of signs such as inappetence associated with the underlying disease (see the article elsewhere in this issue on pancreatitis and diabetes).

SUMMARY

Diabetes is essentially a failure of insulin secretion caused by damage to pancreatic islet β cells. Diabetes in cats is most commonly type 2, which is caused by β-cell failure in the presence of insulin resistance resulting from obesity. The mechanisms of β-cell failure are still debated, but intracellular amyloid oligomers are a likely contributor in the early stages, and glucose toxicity contributes to further β-cell damage and maintenance of the diabetic state. Other causes of β-cell failure include widespread damage to the pancreas by pancreatitis, and diseases of increased insulin resistance such as acromegaly.

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