Canine and Feline Diabetes Mellitus: Nature or Nurture?1

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ABSTRACT There is evidence for the role of genetic and environmental factors in feline and canine diabetes. Type 2 diabetes is the most common form of diabetes in cats. Evidence for genetic factors in feline diabetes includes the overrepresentation of Burmese cats with diabetes. Environmental risk factors in domestic or Burmese cats include advancing age, obesity, male gender, neutering, drug treatment, physical inactivity, and indoor confinement. High-carbohydrate diets increase blood glucose and insulin levels and may predispose cats to obesity and diabetes. Low-carbohydrate, high-protein diets may help prevent diabetes in cats at risk such as obese cats or lean cats with underlying low insulin sensitivity. Evidence exists for a genetic basis and altered immune response in the pathogenesis of canine diabetes. Seasonal effects on the incidence of diagnosis indicate that there are environmental influences on disease progression. At least 50% of diabetic dogs have type 1 diabetes based on present evidence of immune destruction of β-cells. Epidemiological factors closely match those of the latent autoimmune diabetes of adults form of human type 1 diabetes. Extensive pancreatic damage, likely from chronic pancreatitis, causes ~28% of canine diabetes cases. Environmental factors such as feeding of high-fat diets are potentially associated with pancreatitis and likely play a role in the development of pancreatitis in diabetic dogs. There are no published data showing that overt type 2 diabetes occurs in dogs or that obesity is a risk factor for canine diabetes. Diabetes diagnosed in a bitch during either pregnancy or diestrus is comparable to human gestational diabetes. J. Nutr. 134: 2072S–2080S, 2004.

KEY WORDS: • diabetes • dogs • cats • genetic • environmental influences

Feline diabetes: nature or nurture?

The incidence of diabetes in cats ranges from 1 in 50 to 1 in 400 depending on the population studied (2,3). Recent evidence suggests that the incidence is increasing because of an increase in the frequency of predisposing factors such as obesity and physical inactivity (4). Although the incidence in cats is substantially lower than in humans, it is hypothesized to be much higher if the same diagnostic criteria were applied to cats (5). In human diabetics, diagnosis is based on fasting blood-glucose concentration values of ≥7 mmol/L, whereas in cats, it is usually diagnosed once clinical signs are evident (1). This occurs when blood glucose concentration exceeds the renal threshold, which is ~16 mmol/L in healthy cats (6).

Based on histological findings and clinical characteristics, type 2 diabetes accounts for 80–95% of feline diabetes (7). Other specific types of diabetes account for ~15–20% of cases (8,9) and are caused by a variety of diseases that either decrease β-cell numbers or cause marked insulin resistance. The most common diseases that produce diabetes by decreasing β-cell numbers are pancreatic adenocarcinoma and pancreatitis (10). Diseases that produce marked insulin resistance include acromegaly (growth hormone excess), and more moderate insulin resistance results from hyperadrenocorticism and hyperthyroid-
ism. Little is known about the environmental or genetic causes of diseases that produce other specific types of diabetes in cats.

**Cause of type 2 diabetes**

Type 2 diabetes has a complex etiology and is caused by a combination of genetic factors and environmental interactions, and risk increases with aging (11,12).

**Genetic factors in type 2 diabetes**

The susceptibility to type 2 diabetes in humans, monkeys, and rodents is inherited, and preliminary data support a genetic influence in cats (12). Diabetes is most common in domestic long- and short-hair cats. Burmese cats are overrepresented, and many other pure breeds are underrepresented, compared to the incidence in domestic cats. The Burmese breed is overrepresented in Australia, New Zealand (13,14), and the UK (personal communication, D. Gunn-Moore, 2002). The frequency of diabetes in the Burmese breed is approximately four times the rate in domestic cats in Australia, with 1 in 50 Burmese affected compared with <1 in 200 domestic cats (2). In some Burmese families, >10% of the offspring are affected (14). The genetic factors that predispose cats to diabetes are unknown. In Burmese cats, the inheritance is not sex linked or dominant (14). Preliminary results of histological examination of pancreatic tissue show a similar range of islet pathology in diabetic Burmese and diabetic domestic cats, which suggests that the mutation does not directly result in excessive deposition of islet amyloid polypeptide or another metabolic product causing destruction of β-cells (personal communication, R. Lederer, 2003). Limited data available suggest the genes involved may influence insulin sensitivity (unpublished data, J. Rand, 2003).

Ethnicity is a risk factor in humans, and a very high prevalence of type 2 diabetes occurs in some indigenous populations such as American Indians, Australian Aboriginals, and Pacific Islanders. This genetic predisposition of some ethnic groups is most apparent when combined with a Western lifestyle (15). Underlying insulin resistance (low insulin sensitivity) is thought to be associated with a “thrifty gene” (16), which once enabled hunter-gatherers to utilize food efficiently, but is disadvantageous when combined with an affluent lifestyle. Cats have undergone similar lifestyle changes to the ethnic groups predisposed to diabetes, as they have evolved from hunters to suburban indoor cats and are no longer dependent on hunting to supply their nutritional needs.

**Age and type 2 diabetes**

Increasing age in domestic and Burmese cats is a risk factor for type 2 diabetes, and most cats are >8 y of age with a peak incidence between 10 and 13 y of age (2,3). Although 1 in 50 Burmese cats has diabetes, the incidence increases to 1 in 10 for Burmese cats ≥8 y of age (2). Type 2 diabetes also occurs most commonly in older human patients. As β-cell function declines with age, the risk of overt disease increases (17). Because of the marked increase in obesity and physical inactivity in children (18), 30% of new cases of human type 2 diabetes now occur in people <20 y of age.

**Environmental factors predisposing to type 2 diabetes**

Environmental factors are important in increasing the risk of feline diabetes. They are also very important in the development of human type 2 diabetes and relate to lifestyle, particularly obesity and physical inactivity. Data largely from domestic short- and long-hair cats in North America and Burmese cats in Australia identified obesity, advancing age, male gender, being neutered, and drug treatment as risk factors (3,19,20).

**Role of insulin resistance in type 2 diabetes**

Type 2 diabetes results from impaired insulin secretion combined with impaired insulin action, which is also referred to as decreased insulin sensitivity or insulin resistance (21). Insulin sensitivity is defined as the decrease in glucose for a given amount of insulin. Insulin resistance refers to markedly decreased insulin sensitivity (21).

The ability of insulin-resistant individuals to compensate for reduced insulin sensitivity by increasing insulin secretion largely determines the degree to which their glucose tolerance can be prevented from deteriorating (22). In individuals where this balance cannot be maintained, impaired glucose tolerance and overt diabetes ensues.

Overt diabetes is the result of β-cell failure. It is hypothesized that the major cause of β-cell failure is a prolonged and increased demand on the β-cell to secrete insulin secondarily to insulin resistance (21,23). This leads to β-cell damage, in part mediated by oxidant damage, that triggers apoptosis or programmed cell death. Other factors that adversely affect β-cell numbers and function include islet amyloid deposition (24), glucose toxicity (25), pancreatitis (8), and certain dietary influences (26).

Because insulin resistance requires increased insulin secretion to maintain euglycemia, which over time also leads to β-cell failure, it is a core abnormality in type 2 diabetes. Many factors contribute to insulin resistance including genotype, obesity, physical inactivity, drugs, illness, hyperglycemia, and gender.

**Genetic influences on insulin sensitivity**

In cats, we have shown (27) that with an average of 44% body weight gain, nearly 50% of healthy cats develop impaired glucose tolerance. Interestingly, lean cats that developed impaired glucose tolerance with weight gain already had on average 35% lower insulin sensitivity than cats that maintained normal glucose tolerance after gaining weight. In fact, having an insulin sensitivity index below the reference-range median resulted in a threefold increased risk of developing impaired glucose tolerance with weight gain. These results indicate that normal-weight cats with underlying low insulin sensitivity are at greater risk of developing impaired glucose tolerance if they become overweight or obese. Human patients with impaired glucose tolerance progress to type 2 diabetes at a rate of up to 6% per year (28). It is interesting to speculate whether the underlying low insulin sensitivity in our lean cats, which increased their risk of impaired glucose tolerance with obesity, was genetically determined as it is in people. In human patients, insulin resistance is largely the result of genotype but is worsened by environmental factors such as obesity (21,29). In fact, insulin resistance is present in ~25% of nonobese people with normal glucose tolerance (30). If these individuals gain weight, some will no longer be able to secrete enough insulin to compensate for the additional deterioration in insulin resistance that accompanies weight gain. In this situation, decompensation of glucose metabolism occurs, and impaired glucose tolerance develops.

Importantly, our results suggest that some cats have an underlying predisposition to develop glucose intolerance, and if
these cats become obese, they may be at greater risk of developing overt type 2 diabetes over time. Preventative programs aimed at reducing body weight and improving insulin sensitivity would be most effective if directed at cats with underlying low insulin sensitivity.

**Insulin resistance, evolution, and diet**

Insulin resistance is frequent in indigenous populations that have a high incidence of diabetes. This raises the question whether insulin resistance has an evolutionary advantage. Two theories have been proposed to explain the high frequency of insulin resistance and diabetes in these populations. The “thrifty gene” theory proposes that selective resistance to the glucose lowering but not the fat forming effects of insulin facilitated the efficient conversion of energy to fat when food was plentiful. When food was scarce, the fat store was utilized and insulin resistance maintained glucose levels (16).

The “carnivore connection” theory proposes that resistance to the glucose-lowering effects of insulin evolved during the Ice Age to maintain euglycemia on a high-protein, low-carbohydrate diet (26). Inherited insulin resistance in conjunction with environmental risk factors such as physical inactivity, obesity, and consumption of excessive amounts of highly refined, easily digestible carbohydrates places a large, prolonged demand on the β-cells for excessive insulin secretion, which eventually results in β-cell exhaustion and diabetes.

Recent evolutionary history of cats parallels that of modern human populations, particularly the recently urbanized indigenous populations that have very high incidences of insulin resistance and diabetes. Although cats evolved as strict carnivores, many commercial diets are moderate to high in carbohydrates (>50% of calories). This change from a low-carbohydrate, high-protein diet typical of feral cats to a high-carbohydrate diet has only become widespread in the last 20–30 y and may be partially responsible for the recent increase in incidence of diabetes in domestic cats. This change in diet has also been accompanied by a shift from an outdoor environment to indoor confinement and decreased physical activity, because cats no longer need to hunt to obtain nutrition. If these theories were true for cats, possessing the thrifty genotype would confer a survival advantage in times of inconsistent or limited food supply but would be disadvantageous when there is a consistent supply of highly palatable, energy-dense food.

**Obesity and insulin resistance**

The major acquired risk factor for type 2 diabetes in other species is insulin resistance associated with obesity. Even small increases in body-mass index and fat-cells sizes have been associated with a significant increase in the risk of developing diabetes (31). Obesity is also a significant risk factor for diabetes in cats (3,19,32). This increased risk is the result of obesity-induced insulin resistance and hyperinsulinemia (21,27). In a recent study (27), free access to a highly palatable, energy-dense diet over ~10 mo resulted in cats increasing their bodyweight by a mean of 1.9 kg or 44.2%. Insulin sensitivity was reduced by more than half with weight gain in these cats. In fact, in two thirds of the cats, insulin sensitivity fell below the range previously reported for normal cats (33). These results concur with studies on human patients, which report a decrease in insulin sensitivity of between 44 and 72% in obese subjects compared with normal-weight control subjects (34–37). Importantly, after weight gain, 25% of the cats in our study had an insulin sensitivity value that lay within the range previously reported for diabetic cats (33). Fasting hyperinsulinemia in lean cats was the greatest single risk factor for the development of impaired glucose tolerance with obesity.

The pattern of fat deposition in obese individuals also influences the severity of insulin resistance. In general, central obesity (abdominal obesity) in humans is associated with greater insulin resistance and risk of diabetes than peripheral obesity (38). Interestingly, overweight Burmese cats typically develop abdominal fat rather than the subcutaneous inguinal fat found in overweight domestic cats (unpublished observation, J. Rand, 2003).

**Physical inactivity and insulin resistance**

Physical inactivity increases the risk of human type 2 diabetes both directly by decreasing insulin sensitivity and indirectly by an effect on body weight (39,40). Inactive dogs are also insulin resistant. In Burmese cats, being confined indoors and having a low physical activity score were significant risk factors for diabetes (20). If the modern lifestyle of an urban cat is compared with a feral cat that hunts to obtain all its food, urban cats, especially cats confined indoors, are very physically inactive. They no longer hunt for food or fight and are therefore also likely to be insulin resistant. Increasing physical activity in cats by 10 min of daily play produced as much weight loss as calorie restriction (41).

**Drugs and insulin resistance**

Veterinarians can contribute to loss of insulin sensitivity by prescribing drugs that cause insulin resistance, especially if these medications are used long term or if long-acting forms are chosen. A wide variety of pharmacological agents such as corticosteroids are known to be diabetogenic in people. Corticosteroids and progestins (42) are the most commonly used drugs in cats that cause insulin resistance. Two or more treatments with corticosteroids in the 2 y preceding diagnosis of diabetes were a significant risk factor for diabetes in Burmese cats (20) and are reported as a risk factor in domestic cats (43,44). A trend for diabetic Burmese cats to have been treated with megestrol acetate approached significance.

**Illness and insulin resistance**

Dental disease was a significant risk factor for diabetes in Burmese cats as were chronic or recurring medical problems (20). Anecdotally, treatment for periodontal disease is often associated with improved glycemic control in diabetic cats and sometimes a reduction in insulin dose. Inflammation may also play a pathogenic role in human type 2 diabetes (45–47), and periodontal disease and diabetes tend to promote one another (48). It is thought that illness decreases insulin sensitivity, and evidence suggests that insulin therapy is helpful in maintaining euglycemia even in nondiabetic patients (49).

**Gender and insulin resistance**

Male cats have a greater risk for developing diabetes than female cats (3,13,32). The reason for this increased risk may be related to two factors. The first is the tendency of male cats to have lower insulin sensitivity values (37% lower) than females when they are lean, which deteriorates further with weight gain (27). Similarly, when obese, male cats also tend to have lower insulin sensitivity than female cats. Interestingly, only male cats had significantly increased basal insulin concentrations after weight gain, and the absolute concentrations tended to be higher than in obese female cats. Data for other species suggests...
that low insulin sensitivity contributes to obesity by shifting energy metabolism from muscle to fat as hypothesized by the thrifty gene theory (16).

Second, male cats are predisposed to obesity (50–52). In our study (27), cats were allowed free access to food over ~10 mo. Male cats gained more weight (54 vs. 39% body weight) and were significantly heavier after weight gain than female cats (7.26 vs. 5.69 kg), although their initial body weights were not significantly different (4.78 vs. 4.12 kg) (27). Male cats also had a significantly higher fat mass (3.2 vs. 2.3 kg) and lean body mass (4.1 vs. 3.4 kg) compared with female cats, which reflected their higher weight gain. Our study also showed that the greater the fat mass, the less effective insulin was in reducing plasma glucose. These findings of lower insulin sensitivities and higher insulin concentrations in male cats may explain why male cats have a greater risk of developing obesity and diabetes than female cats (3). Excess energy intake, obesity, and inactivity may contribute to or interact with these underlying defects in male cats and ultimately lead to the development of diabetes.

**Diet and development of type 2 diabetes**

Traditionally, human diets recommended for the prevention of obesity and diabetes were rich in readily digestible carbohydrates and fiber and low in fat (53). Recently, this recommendation has been questioned. It is hypothesized that chronic ingestion of a high-carbohydrate diet promotes obesity and increases the demand on β-cells for insulin secretion, thereby predisposing individuals to hyperinsulinemia, apoptosis, β-cell failure, and development of type 2 diabetes (21).

The effects of dietary macronutrients were recently evaluated in healthy cats (54). Three test diets were used that were high in protein (46% of energy), fat (47% of energy), or carbohydrate (46% of energy). The two lesser macronutrients contributed approximately equally to energy. Cats fed the high-carbohydrate diet had significantly higher mean and peak (23–32%) glucose concentrations and tended to have higher insulin concentrations than cats fed either the high-protein or the high-fat diet (54). Consequently, feeding a high-protein, low-carbohydrate, moderate-fat diet to cats at risk of diabetes may be beneficial. Feeding diabetic cats a very low-carbohydrate, high-protein diet improved hyperglycemia, reduced insulin dosage, and increased the rate of diabetic remission (55).

Although diet was not found to be a significant risk factor in the study of 66 Burmese cats, diets supplemented with high-protein, low-carbohydrate foods such as meat or fish approached significance in protecting against diabetes (20). There was a trend in Burmese cats for diabetes to be associated with treatment for renal disease, which typically includes a restricted-protein, high-carbohydrate diet. Owners of diabetic Burmese cats also tended to describe the cat as a "greedy eater." A direct nutritional role in human type 2 diabetes is evident from large epidemiologic studies and it is important in primate and rodent models of the disease (56).

**Carbohydrate source and diabetes**

Ingestion of different sources of carbohydrate (such as rice) has been shown to increase the demand for insulin in cats and could potentially contribute to β-cell failure in susceptible cats when fed long term. The impact of the dietary carbohydrate source on food intake, glucose and insulin concentrations, and insulin sensitivity in overweight cats with reduced insulin sensitivity was assessed (57) using two diets formulated to contain similar starch content (33%) from different cereal sources (sorghum and corn vs. rice). When compared with the sorghum/corn-based diet, cats fed the rice-based diet consumed more energy and gained more weight in response to free-access feeding. Cats fed the rice-based diet also tended to have higher blood glucose concentrations and insulin secretion in response to a glucose load or a test meal.

Foods that produce relatively rapid and high postprandial glucose and insulin responses (high glycemic index foods) have been associated with lessened satiety and greater subsequent food intake in people (58–60). Thus, consumption of high glycemic index foods may lead to increased hunger and promote overeating and weight gain. As carnivores, feral cats consume high levels of dietary protein and are not naturally adapted to eating large quantities of dietary carbohydrate (61). It could be theorized that feeding cats a high-carbohydrate diet, particularly if it is sourced from rice, may result in increased insulin secretion and lead to reduced satiety and increased food intake. When fed over the long term, such a diet could be considered a factor in the etiology of feline obesity and may contribute to the maintenance of excess body weight in overweight cats. In some cats, particularly those with underlying low insulin sensitivity, life-long consumption of a high glycemic index diet (such as a rice-based diet) may also contribute to premature β-cell "burnout" and diabetes by increasing the animals’ overall demand for insulin secretion. Feeding a diet with a low glycemic load may exert a protective role against the development of obesity, impaired glucose tolerance, and diabetes, and may prove beneficial for managing feline obesity and diabetes.

**Dietary supplements and development of diabetes: chromium**

Chromium is an essential trace element that is required for normal carbohydrate and lipid metabolism (62). It is thought (63) that chromium improves glucose tolerance by increasing insulin sensitivity: with greater insulin effectiveness, blood glucose concentrations decrease.

We recently investigated (64) the effect of dietary chromium supplementation on glucose and insulin metabolism in healthy, nonobese cats. Results demonstrated that the incorporation of chromium tripicolinate at 300 and 600 parts per billion in the ration of healthy cats produced small but significant improvements in glucose tolerance as measured by glucose half-life, area under the glucose curve, and absolute glucose concentrations.

Based on the understanding that chromium is an essential nutrient and not a therapeutic drug, only individuals with suboptimal chromium nutrition would be expected to respond to chromium supplementation (65). However, >90% of typical diets consumed by people in the USA contain daily chromium concentrations below the recommended minimum daily intake for dietary chromium level (66). Presently, there are no guidelines for recommended daily chromium intake in cats (67). Before and during the trial, cats in our study consumed complete and balanced diets that met the Association of American Feed Control Officials standards for adult maintenance, and were expected to contain adequate chromium levels. However, the response in our study suggests that cats that consume such diets may still have marginal chromium intake and may benefit from supplementation.

Because of its trend to improve glucose tolerance, cats most likely to benefit from chromium supplementation are those with glucose intolerance and insulin resistance from lack of exercise, obesity, and old age; cats with underlying low insulin...
sensitivity; or cats that are genetically at risk of diabetes (e.g., Burmese cats) (13,14).

Conclusion

Strong evidence exists in cats to suggest that diabetes is the result of a combination of genetic and environmental factors. Obesity, physical inactivity, diet, concurrent illness, and drug intake appear to be the most common predisposing factors. Genetic factors play a role in feline diabetes, but the genes involved are still to be elucidated. It is likely that the genes will be first identified in Burmese cats based on evidence of their genetic predisposition.

Canine diabetes: nature or nurture?

Diabetes mellitus is one of the most frequent endocrine diseases affecting middle-aged and older dogs, and the prevalence is increasing. Thirty years ago, 19 in 10,000 dogs visiting veterinary hospitals were diagnosed with diabetes (68,69). By 1999, the prevalence in the same veterinary hospitals had increased threefold to 58 per 10,000 dogs (69). At present, there are no internationally accepted criteria for the classification of canine diabetes. No laboratory test is readily available to identify the underlying cause of diabetes in dogs, and diagnosis is generally made late in the disease course. If the criteria established for human diabetes are applied to dogs, at least 50% of diabetic dogs would be classified as type 1, because this proportion has been shown to have antibodies against β-cells (70–72). The remainder probably has “other specific types of diabetes” that result from pancreatic destruction or chronic insulin resistance, or they have diestrus-induced diabetes.

Cause of type 1 diabetes

Type 1 diabetes appears to be the most common form of diabetes in dogs, and is characterized by pancreatic β-cell destruction that leads to absolute insulin deficiency. In people, this usually occurs via cell-mediated autoimmune processes and is associated with multiple genetic predispositions and poorly defined environmental factors (1). Similar to canine diabetes, the incidence rate of type 1 diabetes in people is rising (73), a trend that has been explained on the basis of increased contacts with adverse environmental factors acting on a background of complex genetic factors (74). The rate of progression to absolute insulin deficiency is quite variable in humans. It can be rapid in young children and much slower in middle-aged and older people. This latter group has the latent predisposition. Other specific types of diabetes" that result from pancreatic destruction or chronic insulin resistance, or they have diestrus-induced diabetes.

Environmental factors in type 1 diabetes

Although genetic susceptibility appears to be a prerequisite in type 1 diabetes, multiple environmental factors likely initiate β-cell autoimmunity, which, once begun, proceeds by common pathogenic pathways (74). β-Cell autoimmunity probably propagates continuing destruction of β-cells and prevents islet cell regeneration after injury (90). Although the rate of progression is irregular, accelerated β-cell destruction may occur just before diagnosis (74). This may be due to environmental influences, because human type 1 diabetes is diagnosed more frequently in autumn and winter (91,92). Interestingly, a highly significant seasonal incidence of diagnosis of canine diabetes also exists and the incidence peaks in winter (93).

Specific environmental risk factors have not yet been evaluated in diabetic dogs, and prospective epidemiological investigation of affected animals and age-matched nondiabetic controls is indicated. The association between canine diabetes and pancreatitis warrants particular attention, because β-cell autoimmunity, pancreatic inflammation, and regulation of gut immunity may be linked in disease pathogenesis. The gut immune system likely plays a central role in the pathogenesis of type 1 diabetes, because accumulating evidence suggests that
affected people have aberrant regulation of gut immunity (94,95). The gut and the pancreas are probably immunologically as well as anatomically linked and influenced by environmental factors such as intestinal microflora, infections, and dietary factors (94). Two environmental risk factors that are frequently implicated in type 1 diabetes, enteroviral infections and exposure to cow’s milk proteins, both trigger the gut immune system (95).

**Association between diabetes and pancreatitis in dogs**

Extensive pancreatic damage, which likely results from chronic pancreatitis, is responsible for the development of diabetes in ~28% of diabetic dogs (83). Chronic pancreatitis is recognized as a distinct cause of diabetes in people, because affected insulin-dependent individuals do not have the immunological phenomena or the association with leukocyte antigen alleles that characterize type 1 diabetes (96). Lack of humoral immunity may contribute to the slower rate of destruction of B-cells in people with chronic pancreatitis compared with those with type 1 diabetes (97). The rate of progression of B-cell loss is being investigated in dogs with chronic pancreatitis using sequential glucagon-stimulation tests (84). Preliminary findings indicate that some dogs with chronic pancreatitis have reduced B-cell function and appear to be prediabetic.

Although extensive pancreatic damage is responsible for the development of diabetes in 28% of diabetic dogs, evidence of acute or chronic pancreatitis is found in a larger proportion (~40%) of diabetic dogs (81,98–104). It is possible that pancreatitis plays a role in the development of B-cell autoimmunity in genetically susceptible dogs or, alternatively, the diabetic state may be a risk factor for pancreatitis. Hypertriglyceridemia was proposed as a possible inciting cause of canine pancreatitis (105) and is commonly seen in diabetic dogs (81). Comparison of the incidence of pancreatitis in diabetic dogs with that of age-matched nondiabetic dogs would help to clarify its role in the pathogenesis of canine diabetes.

Obesity affects one quarter to one third of dogs presented to veterinary practices (106–108) and is associated with an increased risk of pancreatitis (104). As pancreatitis appears to be a common cause of diabetes in dogs (83), this relationship between obesity and pancreatitis in dogs has relevance to the pathogenesis of canine diabetes. Environmental factors such as the feeding of high-fat diets that result in lipemia and disturbances in lipid metabolism are implicated as potential etiological factors in dogs with obesity-associated pancreatitis (109) and likely play a role in the development of pancreatitis in diabetic dogs.

**Role of insulin resistance in canine diabetes**

Diabetes induced by insulin-resistance states are less common “other specific types” of canine diabetes. Disease conditions such as hyperadrenocorticism (110) and acromegaly (111) result in insulin resistance and may induce diabetes in dogs. Intravenous causes of insulin resistance that may lead to induced diabetes include chronic corticosteroid therapy (112). As most dogs do not develop overt diabetes with chronic corticosteroid therapy or spontaneous hyperadrenocorticism, for overt diabetes to develop may require underlying reduced B-cell function that results from immunological processes or chronic pancreatitis.

**Obesity-induced insulin resistance in dogs**

There are no well-documented studies that convincingly demonstrate that type 2 diabetes is a significant disease entity in dogs.

Although obesity causes insulin resistance in dogs, there are no published data that clearly indicate obesity is a risk factor for canine diabetes. No epidemiological data examining the relationship between canine diabetes and obesity have been published since 1960 (113), and an association between obesity and diabetes in dogs is not presently recognized. Obesity is a well-established risk factor for type 2 diabetes in cats and people. In contrast, dogs are not reported to develop a form of diabetes analogous to type 2 diabetes. In dogs, obesity causes insulin resistance (114–116), which leads to hyperinsulinemia and impaired glucose tolerance (117,118). These effects are particularly pronounced when obesity is induced by feeding a diet high in saturated fat (119). Dogs fed a high-fat diet develop insulin resistance that is not compensated for by increased insulin secretion, resulting in more severe glucose intolerance (120). Despite the evidence that obesity causes impaired glucose tolerance, it appears that very few dogs develop overt diabetes as a consequence of obesity-induced insulin resistance.

There are no published studies investigating whether obesity is a risk factor for dogs with absolute insulin deficiency, which represent the majority of diabetic dogs. The only study to examine the effects of obesity in diabetic dogs used animals with relative insulin deficiency (117). Unfortunately, the study used mostly intact bitches. Because 13 of the 15 diabetic dogs with residual B-cell function were female and most if not all were intact females, they most likely had diestrus-induced diabetes rather than type 2 diabetes (117,121). The study reported that obesity caused insulin resistance that resulted in hyperinsulinemia and glucose intolerance, but these findings were confounded by the insulin resistance associated with elevated progesterone and growth hormone concentrations that occurs in intact bitches. Therefore, the effect of obesity-induced insulin resistance cannot be separated from diestrus-induced insulin resistance in this study. Investigation of the role of obesity in diabetic dogs with no underlying diestrus- or hyperadrenocorticism-associated insulin resistance still needs to be performed.

**Diestrus- and gestation-associated diabetes**

Gestational diabetes is another classification of diabetes recognized in humans. In women, it is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (1). If overt diabetes persists after the pregnancy ends, then it is reclassified as type 1, type 2, or another specific type of diabetes. Reduced insulin sensitivity occurs in healthy bitches by d 30–35 of gestation (122) and becomes more severe during late pregnancy (123). The diestrus phase of the nonpregnant cycle of the bitch is similar in duration to the 9 wk of pregnancy, and it is generally agreed that the hormone profiles during diestrus and pregnancy are essentially identical (123–125). However, the reduction in insulin sensitivity is more pronounced during pregnancy than during diestrus (122), and the alteration in the metabolic control of growth hormone during gestation may in some way be pregnancy-specific in dogs (123). Nevertheless, progesterone elevation does cause glucose intolerance and overt diabetes during diestrus in bitches (126,127). Progesterone also stimulates the mammary gland of bitches to produce growth hormone, which is a potent inducer of insulin resistance (111). Consequently, if diabetes is
diagnosed in a bitch during either pregnancy or diestrus, it probably should be classified as being comparable to human gestational diabetes. If diabetes persists after the pregnancy or diestrus ends, then it should be reclassified as type 1 or another specific type of diabetes. The periodic influence of diestrus-associated insulin resistance may contribute to the increased risk for developing diabetes in female compared with male dogs (68,69) and highlights the role that environmental influences may play in the pathogenesis of canine diabetes.

Juvenile-onset diabetes in dogs

An inherited early-onset form of diabetes characterized by abiotrophy of islet β-cells in a line of Keeshond dogs (128), is a rare example of an “other specific type” of canine diabetes and presumably has a genetic basis.

Summary of canine diabetes: nature or nurture

Classification of canine diabetes based on the criteria established for human diabetes can be summarized as follows: type 1 diabetes (likely analogous to the human LADA form of type 1 diabetes), other specific types of diabetes, and diestrus or gestational diabetes.

Evidence is mounting for a genetic basis for canine diabetes, and the association with the major histocompatibility complex alleles on the dog leukocyte antigen gene strongly suggests that the immune response has a role in pathogenesis. At least 50% of diabetic dogs have type 1 diabetes based on present evidence of immune destruction of β-cells. Epidemiological factors closely match those of human patients with the LADA form of type 1 diabetes. Multiple environmental factors likely initiate β-cell autoimmunity, which, once begun, proceeds by common pathogenic pathways. There is a highly significant seasonal incidence of diagnosis of canine diabetes with the incidence peaking in winter, which indicates that environmental influences have a role in disease progression just before diagnosis.

Extensive pancreatic damage that likely results from chronic pancreatitis is responsible for the development of diabetes in ~28% of diabetic dogs and thus is the most common “other type” of diabetes in dogs. There is no evidence that type 2 diabetes occurs in dogs or that obesity is a risk factor for canine diabetes. There is evidence that obesity is a risk factor for canine pancreatitis, which may have relevance to the pathogenesis of canine diabetes, because pancreatitis appears to be a common cause of diabetes in dogs. Environmental factors such as feeding a high-fat diet, which results in lipemia and disturbances in lipid metabolism, are implicated as potential etiological factors in dogs with obesity-associated pancreatitis and likely play a role in the development of pancreatitis in diabetic dogs.

Canine diabetes secondary to corticosteroid therapy, hyperadrenocorticism, or acromegaly constitute less common “other specific types of diabetes.” Diabetes diagnosed in a bitch during either pregnancy or diestrus should be classified as being comparable to human gestational diabetes. The periodic influence of diestrus-associated insulin resistance may contribute to the increased risk of female compared with male dogs for developing diabetes and highlights the role that environmental influences may play in the pathogenesis of canine diabetes.

Specific environmental risk factors have not yet been evaluated in diabetic dogs, and prospective epidemiological investigation of affected animals and age-matched nondiabetic controls is indicated. The association between canine diabetes and pancreatitis warrants particular attention, because β-cell autoimmunity, pancreatic inflammation, and regulation of gut immunity may be linked in disease pathogenesis.

Conclusion

In conclusion, genetic and environmental factors play a role in both canine and feline diabetes. In cats particularly, preventative programs aimed at promoting physical activity and ideal body condition are likely beneficial in reducing the risk of diabetes.

LITERATURE CITED

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