

Feline Models of Type 2 Diabetes Mellitus

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Abstract

Feline diabetes mellitus (FDM) closely resembles human type 2 diabetes mellitus (T2DM) in many respects including clinical, physiological, and pathological features of the disease. These features include age of onset of FDM in middle age, association with obesity, residual but declining insulin secretion, development of islet amyloid deposits, loss of approximately 50% of β -cell mass, and development of complications in several organ systems including peripheral polyneuropathy and retinopathy. Many of the pathological aspects of the disease are also experimentally inducible, facilitating study of the pathogenesis of these lesions. Physiological aspects of FDM and obesity are also well studied in the cat and provide an excellent basis for comparative studies of human T2DM. The relatively short generation time of cats along with breed predispositions to development of FDM may allow for more rapid screening and identification of genetic markers for diabetes susceptibility. FDM, in both spontaneous and inducible forms, therefore provides a good animal model of human T2DM and may provide additional insights into the pathogenesis of this important condition.

Key Words: animal model; feline; islet amyloid; islet amyloid polypeptide; type 2 diabetes mellitus

Introduction

Animal models of type 2 diabetes mellitus (T2DM¹) provide the opportunity to investigate pathogenesis as well as evaluate novel treatment and prevention options for the disease. Much has been learned from models utilizing transgenic or inbred strains of rodents. However, there are benefits in studying spontaneous and induced disease in an outbred population. The domestic cat develops diabetes mellitus that is clinically and pathologically similar

to human type 2 diabetes (Table 1). Because it is the most common household pet, the domestic cat shares the same environment with humans and many of the risk factors for diabetes such as physical inactivity and obesity. The large litter sizes of the cat could allow genetic linkage studies of diabetes that are not possible in humans. The natural lifespan of the cat provides an additional advantage for study of spontaneous disease—being shorter than primates to allow more rapid study of onset, progression, treatment, or prevention, yet longer than rodents to allow study of complications that may take years to develop. In addition, large animal models are a useful complement to rodent models for both practical and physiological reasons. This review summarizes the similarities and differences between human type 2 diabetes and spontaneous and induced diabetes mellitus in the cat.

T2DM is characterized by insulin resistance, defective insulin secretion, islet amyloid formation, and β -cell loss (O'Brien et al. 1885, 1986). In addition to humans and macaques (O'Brien et al. 1996), the domestic cat is one of the few species that develops diabetes with all of these characteristics. Significant ground work has been laid for further evaluating diabetes and glucose metabolism in the cat. Normal, obese, and diabetic cats have been evaluated with a variety of physiological tests including the intravenous glucose tolerance test (Appleton et al. 2001a; Hoening et al. 2002; Nelson et al. 1990; O'Brien et al. 1985) and hyperinsulinemic euglycemic clamp (Petrus et al. 1998), as well as glucagon and arginine stimulation tests (Kirk et al. 1993; Kitamura et al. 1999).

Spontaneous Diabetes Mellitus in the Domestic Cat

Clinical Characteristics

Although rare cases resembling type 1 diabetes have been reported in the cat (Root et al. 1995; Thoresen et al. 2002), the majority of cats with diabetes (>80%) have clinical characteristics and pathological abnormalities consistent with T2DM in humans (Johnson et al. 1986). Depending on the population studied, the incidence of diabetes in cats ranges from one in 50 to one in 400 (Baral et al. 2003; Panciera et al. 1990). Some evidence suggests that the incidence of diabetes in cats is increasing for the same reasons it is increasing in humans—an increase in obesity and a decrease in physical activity (King et al. 1998; Prahel et al. 2003).

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¹Abbreviations used in this article: DSP, distal symmetric polyneuropathy; FDM, feline diabetes mellitus; IA, islet amyloidosis; IAPP, islet amyloid polypeptide; T2DM, type 2 diabetes mellitus; VEGF, vascular endothelial cell growth factor.

Table 1 Comparisons between spontaneous feline diabetes mellitus and human type 2 diabetes mellitus

Parameter	Feline	Human
Age of onset	Middle age (6+ yr)	Middle age
Ketoacidosis	Some	Uncommon
Obesity	Yes	Yes
Insulin (peripheral)	Low but detectable	Variable
Islet amyloidosis	>80%	>90%
β -cell loss	~50%	~40-60%
Peripheral neuropathy	Yes	Yes

Although the typical onset of T2DM in humans is in middle-aged and older individuals, due to obesity and lack of activity, the incidence in younger individuals is increasing (Pinhas-Hamiel and Zeitler 2005; Rosenbloom et al. 1999). Similar to humans, the typical onset for diabetes in the cat is in middle age or older, with the peak incidence occurring between 9 and 13 yr of age (Baral et al. 2003; Johnson et al. 1986; Panciera et al. 1990). Also similar to humans, feline diabetes mellitus (FDM¹) is associated with diseases or drugs that increase insulin resistance, such as acromegaly or hyperadrenocorticism or treatment with corticosteroids or progestagens (Nelson et al. 1990; Peterson 1987; Peterson et al. 1990).

Insulin Resistance

Along with β -cell dysfunction and loss, insulin resistance is critical to the pathogenesis of T2DM. Insulin resistance is the pathological state in which the biological response to insulin is diminished leading to compensatory hyperinsulinemia. Diabetes occurs when the β -cells cannot produce enough insulin to maintain normal blood glucose. Multiple factors contribute to insulin resistance, and those evaluated in the cat are similar to those in humans. For example, obesity is a risk factor for diabetes in cats (Crenshaw and Peterson 1996; Panciera et al. 1990; Scarlett and Donoghue 1998), and weight loss improves glucose tolerance in both species (Fettman et al. 1998; Uusitupa et al. 2003). In humans, genotype is a factor that dictates insulin sensitivity, although the degree of obesity, physical activity, and other environmental factors play a more prominent role (Harris 1995). There is a wide range in insulin sensitivity in the human population. Approximately 25% of nonobese individuals with normal glucose tolerance are insulin resistant (Hollenbeck and Reaven 1987). Cats may be similar in that lean cats with normal glucose tolerance but with insulin sensitivity values below the population median have an approximately three-fold increased risk of developing impaired glucose tolerance after weight gain (Appleton et al.

2001b). It is necessary to replicate this study using mathematical modeling validated for feline physiology rather than extrapolated from human models, but the similarity is intriguing and suggests there may be a genetic component to insulin sensitivity in the cat as in humans. Approximately 6% of humans with impaired glucose tolerance progress to T2DM per year (Harris 1989; Sasaki et al. 1982). The rate of progression from impaired glucose tolerance to diabetes in cats is not known.

Genetics of Type 2 Diabetes

As with insulin sensitivity, genetics play an important role in diabetes risk. Lean relatives of type 2 diabetics are insulin resistant and have increased risk of diabetes (Vauhkonen et al. 1998; Warram et al. 1990). In addition, relatives of diabetics have a reduced β -cell compensatory response to the reduced insulin sensitivity associated with obesity (Elbein et al. 2000). This evidence suggests a genetic predisposition to the β -cell failure in T2DM in addition to the predisposition to insulin resistance. The genetic susceptibility to T2DM is well documented in humans and rodents (Barroso 2005; Kim et al. 1998). Although monogenic disorders have been identified and helpful in elucidating some pathogenetic mechanisms, the majority of diabetes susceptibility appears to be polygenic in nature (Barroso 2005) and therefore much more difficult to evaluate. Studying an age-associated disease such as diabetes is somewhat easier in the cat due to the relatively short lifespan. In addition, the litter size of the cat makes genetic linkage studies easier than in humans. Breed differences provide additional support for a genetic component in the pathogenesis of FDM. In Australia, the frequency of diabetes in the Burmese breed is approximately one in 50, compared with one in 200 domestic cats (Baral et al. 2003; Rand et al. 1997), with some families of Burmese cats having more than 10% of offspring affected (Wade et al. 1999). The predisposition in Burmese cats is not sex linked or dominant (Wade et al. 1999). Other cat breeds are under-represented in the diabetic population relative to domestic short- and long-haired cats (Baral et al. 2003). Thus, the study of differences between breeds may be helpful in identifying genetic risk factors for FDM.

In addition, studying the physiology of the cat, which is an obligate carnivore, may be helpful in understanding the pathogenesis of diabetes in certain human populations. Insulin resistance and diabetes are more frequent in certain ethnic groups including Native Americans, Australian Aborigines, and Pacific Islanders. The "carnivore connection" and the "thrifty gene" theories have been proposed to explain a potential evolutionary advantage to insulin resistance (Miller and Colagiuri 1994; Neel 1962). Both glucose and amino acids promote insulin secretion. The carnivore connection theory proposes that resistance to the glucose-lowering effects, but not the anabolic effects, of insulin evolved during the Ice Age to maintain normal glucose on the high-protein low-carbohydrate diets available (Miller

and Colagiuri 1994). The thrifty gene theory proposes that during cycles of famine and abundance of food, individuals with resistance to the glucose-lowering effects of insulin, but not the fat-producing effects, had an evolutionary advantage. Energy stored when food was plentiful allowed greater survival during times of scarcity (Neel 1962). Parallels can be noted between the indigenous populations at high risk for diabetes and domestic cats. Both species have had an increase in the rate of diabetes in recent decades (Acton et al. 2002; Prael et al. 2003). The highest rates of obesity and diabetes occur in indigenous populations when they adopt a sedentary lifestyle with a Western diet, rich in processed carbohydrates (Ravussin et al. 1994). Likewise, cats have shifted from an outdoor environment with hunting for high-protein meals to an indoor sedentary lifestyle with commercial foods that are moderate to high in carbohydrates.

Pathological Similarities Between Feline Diabetes Mellitus (FDM) and Human Type 2 Diabetes Mellitus (T2DM)

All of the clinical features of feline diabetes described above closely parallel those of human type 2 diabetes and therefore suggest a common pathogenesis. However, the most striking and provocative similarities between human T2DM and FDM are the lesions occurring in the pancreatic islets, namely islet amyloidosis (IA¹) and partial loss of β -cells (Johnson et al. 1986, 1989; O'Brien et al. 1985, 1986, 1993). IA occurs in nearly all spontaneously diabetic cats and has been detected in more than 90% of humans with type 2 diabetes (Johnson et al. 1986, 1989a; O'Brien et al. 1993). IA is therefore a hallmark lesion of both human T2DM and spontaneous FDM. In FDM, IA deposition is associated with an approximately 50% loss of β -cell mass, whereas nondiabetic cats that have IA show a lesser degree of β -cell loss (O'Brien et al. 1986). These findings suggest a linkage between IA and the progressive loss of β -cells in FDM. Similarly, several studies have shown a significant loss of β -cell mass of 40 to 60% in T2DM (Butler et al. 2003; Rahier et al. 1983; Saito et al. 1979; Westermark 1972). Linkage between IA and β -cell loss has been further documented in macaque models of T2DM (de Koning et al. 1993; Hansen and Bodkin 1986; Howard 1986; O'Brien et al. 1996) in which increasing levels of IA deposition are correlated with reductions in β -cell mass. Yet another parallel is found in human patients with diabetes associated with cystic fibrosis (Couce et al. 1996b). IA was shown to be present in 67% of cystic fibrosis patients with diabetes but only in 27% of age-matched nondiabetic patients, and it was associated with a 50% loss of β -cell mass (Couce et al. 1996b). Thus, numerous studies have shown an intriguing linkage between IA and β -cell loss across several species, each of which shares close similarities in clinical and physiological aspects of their particular form of diabetes. Also notable is the lack of IA formation in any form of rodent

diabetes mellitus (except transgenics as discussed below) despite a plethora of "T2DM" models in these species.

Our understanding of the pathogenesis of FDM and human T2DM was greatly advanced by the discovery of the precursor protein of IA, namely islet amyloid polypeptide (IAPP¹) (Cooper et al. 1987; Westermark et al. 1987a,b). IAPP was shown to be a 37 amino acid polypeptide that is produced predominantly by the pancreatic β -cells and is co-packaged with insulin in the β -cell secretory vesicles in both the cat and humans (Johnson et al. 1988; Leffert et al. 1989; Lukinius et al. 1989). The co-localization of IAPP and insulin in the β -cell secretory vesicle implied that they were secreted, and this implication was subsequently confirmed by several studies (Butler et al. 1990; Fehmann et al. 1990; Inoue et al. 1991; O'Brien et al. 1991). IAPP was therefore demonstrated to be a β -cell secretory product of both normal and diabetic animals and humans. This discovery provided the basis for an explosion of subsequent studies into the molecular pathogenesis of IA and associated forms of diabetes mellitus.

As noted above, IA occurs in only certain species (cats, humans, macaques) and notably does not occur spontaneously in rodents. This observation prompted comparisons of amino acid sequence between rodents and species that develop IA to assess for the presence of either primary or secondary structural differences that might explain this difference. These comparisons revealed highly conserved regions in the amino-terminal regions (residues 1-19) and in the carboxy-terminal region (residues 30-37) (Betsholtz et al. 1989). The midsection of the molecule (residues 20-29), however, showed important sequence variations. Secondary structure predictions of this region in humans and cats indicated a high propensity to form β -sheet structure, which is essential in the formation of amyloid fibrils, whereas rodent IAPP did not. Peptides corresponding to human IAPP 20-29 readily form amyloid-like fibrils in aqueous solution, whereas the rodent IAPP 20-29 did not. These findings provided a reasonable explanation for the species restriction in formation of IA but did not explain why some cats and humans developed IA and diabetes.

Because IAPP is a normal secretory product of the β -cell, a further explanation is needed to account for the development of IA from a normal β -cell secretory product. Formation of IA therefore may involve abnormalities in IAPP synthesis, processing, trafficking, secretion, or degradation. The role of increased synthesis of IAPP in amyloidogenesis is supported by several lines of evidence. Importantly, IAPP and insulin are, to a large extent, co-regulated, and production and secretion of both are up-regulated by insulin resistance. Thus, insulin-resistant states that are known to predispose to development of FDM and human T2DM tend to be associated with increased insulin and IAPP production. Cats with impaired glucose tolerance that also have an increased incidence of IA have increased IAPP content versus controls, suggesting increased IAPP production as a precursor to IA development in this species (Johnson et al. 1989b; Ma et al. 1998). Furthermore, under

circumstances of high secretory demand, there is an increase in the amounts of IAPP secreted relative to insulin (Gasa et al. 2001; O'Brien et al. 1991). Thus, prediabetic states in which there is insulin resistance result in increased IAPP and insulin production and secretion, and there may be alteration of the IAPP:insulin ratio. Intriguingly, experiments have shown that insulin tends to inhibit IAPP amyloidogenesis, implying that increasing the IAPP:insulin ratio may favor formation of IA (Charge et al. 1995; Kudva et al. 1998; Westermark et al. 1996). Evidence from several IAPP-transgenic mouse models in which human IAPP is overexpressed also support a role for increased IAPP expression in amyloidogenesis (Couce et al. 1996a; de Koning et al. 1994; Hoppener et al. 2000; Janson et al. 1996; Soeller et al. 1998; Verchere et al. 1996). In each of these transgenic models, the production of high levels of human IAPP by the β -cells was associated with the formation of abnormal IAPP aggregates, selective β -cell loss, and the development of diabetes mellitus. Thus, overexpression of human IAPP in mice led to the development of diabetes mellitus with pathological and clinical features of FDM and human T2DM.

The strong linkage between the development of IA and β -cell loss in FDM and T2DM implies that IA or amyloidogenesis is toxic to β -cells. Experiments using human IAPP transfected COS-1 cells support this hypothesis and showed that human IAPP but not rodent IAPP overexpression in these cells led to formation of amyloid-like fibrils and significant cytotoxicity (O'Brien et al. 1995). The mechanism of cell death was subsequently shown to be by apoptosis (Hiddinga and Eberhardt 1999). In other experimental systems, human IAPP-derived fibrils were shown to be toxic to isolated islets in culture (Lorenzo et al. 1994), neurons, and PC12 cells (Dore et al. 1997; May et al. 1993; Mattson and Goodman 1995). The cytotoxic effects of human IAPP in these systems mimic those of A β (amyloid fibrils of Alzheimer's disease). Importantly, for both IAPP derived amyloid and A β it is the fibrillar forms that are cytotoxic, whereas monomers and related nonamyloidogenic polypeptides are not cytotoxic (Howlett et al. 1995; Lorenzo and Yankner 1994; Schubert et al. 1995). Recent studies, furthermore, indicate that the toxic entities during IAPP amyloidogenesis are early small or intermediate-sized oligomers of IAPP, rather than the large classical amyloid fibrils that appear to be relatively nontoxic (Janson et al. 1999; Lashuel et al. 2002). The mechanism appears to involve the formation of nonselective ion channels in cell membranes leading to apoptosis (Mirzabekov et al. 1996). The findings taken together suggest that the process of IAPP amyloidogenesis involves the formation of toxic molecules during early steps of aggregation that may induce apoptosis of β -cells. Indeed, a recent study of human T2DM patients showed increased rates of β -cell apoptosis in diabetics versus nondiabetic individuals, whereas β -cell replication rate was normal (Butler et al. 2003). Thus, β -cell loss exceeded the rate of regeneration in diabetics and is therefore a likely explanation for the loss of β -cell mass in human T2DM and similar forms of diabetes in cats and macaques.

Experimentally Induced Diabetes Mellitus in the Cat

In addition to spontaneous diabetes, induced-disease models have also been developed in the cat. Unlike rodents, cats are resistant to the diabetogenic effects of streptozotocin and alloxan, yet they remain susceptible to their toxic side effects (Hatchell et al. 1986; Weinstein and Gertner 1971). Partial pancreatectomy alone (>75% removed) or in combination with local injection of alloxan was effective in inducing diabetes in 70% or 100% of cats, respectively (Reiser et al. 1987). These models have been used to evaluate the complications of diabetes rather than the pathogenesis of this disease itself. The induced model that most closely resembles spontaneous diabetes involves partial pancreatectomy (50% removed) combined with growth hormone and dexamethasone treatment to induce insulin resistance (Hoenig et al. 2000). In this study, eight cats were evaluated and all remained hyperglycemic after growth hormone and dexamethasone therapy were discontinued. After a period with diabetes untreated, four cats were treated with insulin and four were treated with the oral hypoglycemic drug glipizide. Glipizide, a sulfonylurea medication, stimulates exocytosis of secretory granules by depolarizing the β -cell, resulting in increased secretion of insulin and IAPP (Inoue et al. 1991; Rajan et al. 1990; Sturgess et al. 1985). During treatment, plasma IAPP concentrations were significantly higher (3- to 5-fold) in the glipizide-treated cats compared with the insulin-treated cats despite similar glycosylated hemoglobin concentrations. At necropsy after 18 mo of treatment, one of four cats in the insulin-treated group had mild amyloid deposits (16% of islets positive), whereas four of four cats in the glipizide-treated group had IAPP-immunoreactive amyloid (87, 33, 2, and 81% of islets positive). Pretreatment pancreatic biopsies were normal in all cats, with no evidence of islet amyloidosis at that time. Thus, this is the first reported model of induced diabetes to develop islet amyloidosis in a nontransgenic animal (Hoenig et al. 2000). This study also raises the possibility that glipizide therapy may promote, or insulin therapy may prevent, formation of islet amyloid deposits.

Diabetic Complications

Due to the many similarities between diabetes in the domestic cat and humans, some of the complications of diabetes have also been studied in the cat. The most thoroughly evaluated diabetic complications are diabetic neuropathy and retinopathy, which are described below.

Diabetic Polyneuropathy

The polyneuropathy associated with type 1 and type 2 diabetes in humans is the most common form of neuropathy in the developed world, affecting approximately 30 to 50% of

all diabetics (Shaw and Zimmet 1999). Diabetic neuropathy can affect different parts of the nervous system and result in a variety of clinical syndromes. The most common syndromes include chronic sensorimotor distal symmetric polyneuropathy (DSP¹) and several autonomic neuropathies (Boulton et al. 2005). The severity and type of symptoms vary widely between patients. Symptoms of DSP range from burning, stabbing, or aching pain to decreased sensation and numbness of the extremities. Decreased sensation in the feet increases the risk for injury and foot ulceration. More than 80% of amputations follow foot injury or ulceration, making DSP a significant source of morbidity for diabetic patients (Boulton et al. 2005). The autonomic neuropathies also cause significant morbidity, most commonly associated with gastrointestinal, urogenital, and cardiovascular dysfunction (Boulton et al. 2005). In addition, reduced cardiovascular autonomic function is strongly associated with increased risk of silent myocardial ischemia and mortality in diabetics (Maser et al. 2003).

Considering the significance of the problems caused by diabetic neuropathies, animal models are needed to advance our understanding of the pathogenesis of these disorders as well as to evaluate potential treatment options. Both rodents with experimental diabetes and cats with spontaneously occurring diabetes develop neurological complications (Kramek et al. 1984; Mizisin et al. 1998, 2002; Sima and Sugimoto 1999). However, because the structural changes associated with diabetic neuropathy in humans may take decades to develop and are recognized initially in the longest nerves, the longer-lived cat with relatively long peripheral nerves may provide opportunities for study not possible in rodents.

The symptoms associated with diabetic neuropathy in the cat include a plantigrade stance, less frequently a palmarigrade stance, posterior paresis, postural reaction deficits, depressed patellar reflexes (Kramek et al. 1984; Mizisin et al. 2002), and increased flinching in response to light touch (Wolff 1984). Similar to changes noted in human diabetics (Arezzo and Zotova 2002; Behse et al. 1977; Islam et al. 2005), electrophysiological abnormalities noted in both the pelvic and thoracic limbs of feline diabetics include decreased nerve conduction velocities and increased F wave and cord dorsum potential latencies (Mizisin et al. 2002). Electromyographic abnormalities were minimal or absent except in the most severely affected animals. When present, the changes were consistent with denervation (Kramek et al. 1984; Mizisin et al. 2002). The pelvic limb appeared to be more severely affected than the thoracic limb, and motor nerve conduction was affected more severely than sensory nerve conduction (Mizisin et al. 2002).

Structurally, the most significant change associated with diabetes in cats is Schwann cell injury resulting in myelin splitting, ballooning, and subsequent demyelination (Mizisin et al. 1998, 2002). The reactive, degenerative, and proliferative changes seen in the Schwann cells of diabetic cats are similar to those seen in human diabetic neuropathy (Kalichman et al. 1998). Additional structural abnormalities

noted in diabetic cats include a decrease in average myelinated nerve fiber density, axonal dwindling, and scattered axonal degeneration, particularly in cats with severe neurological dysfunction (Dahme et al. 1989; Kramek et al. 1984; Mizisin et al. 1998, 2002). Similar but more severe axonal changes have been the focus of research in human diabetic neuropathy (Behse et al. 1977; Malik et al. 2005), but Schwann cell abnormalities appear to precede the axonal changes (Malik et al. 2005). Therefore, diabetic neuropathy in the domestic cat may serve as an excellent model for the pathogenesis and treatment of early diabetic neuropathy in humans.

Several mechanisms are thought to play a role in the tissue-damaging effects of hyperglycemia. One of the most studied mechanisms is increased flux through the polyol pathway. A key enzyme in the polyol pathway is aldose reductase, which normally has the function of reducing toxic aldehydes in the cell to inactive alcohols. However, during hyperglycemia, aldose reductase also reduces glucose to sorbitol, which is then oxidized to fructose by sorbitol dehydrogenase (Brownlee 2001). Aldose reductase inhibitors have ameliorated the functional and structural defects associated with experimental diabetes in rodents and dogs (Engerman et al. 1994; Mizisin et al. 1997; Tomlinson et al. 1994). While reducing excess glucose to sorbitol, aldose reductase consumes the cofactor NADPH, which is also required for regeneration of reduced glutathione, a critical intracellular antioxidant. Thus, increased polyol pathway flux contributes to tissue damage by increasing susceptibility to intracellular oxidative stress (Brownlee 2001). Similar to humans and rodents, increased polyol pathway flux has been documented in spontaneous feline diabetes. However, instead of accumulating sorbitol in nerves as humans do, diabetic cats have a 12-fold increase in nerve fructose relative to nondiabetic controls, presumably due to increased activity of sorbitol dehydrogenase (Mizisin et al. 2002). In addition to the damaging effects of increased polyol pathway flux, excess fructose contributes to production of advanced glycation end products (Sakai et al. 2002), another mechanism by which chronic hyperglycemia may damage tissues. Thus, diabetic neuropathy in humans and cats share multiple electrophysiological, pathological, and biochemical similarities making the feline diabetic an excellent model of the condition in humans.

Diabetic Retinopathy

In addition to the nervous system, diabetes-associated damage has been evaluated in the ocular tissues of the cat. In contrast to other animal models of diabetes, the ocular lens of the adult cat is resistant to the development of diabetic cataracts (Richter et al. 2002; Salgado et al. 2000). This characteristic allows good evaluation of the fundus for study of diabetic retinopathy. Using retinal photography and fluorescein angiography every 6 mo over a 9-yr period, pancreatectomized cats maintained with poor glycemic control

(blood glucose 200–400 mg/dL) developed many of the retinal abnormalities common in diabetic retinopathy in humans (Budzynski et al. 2005; Hatchell et al. 1995; Linsenmeier et al. 1998). The changes included early non-leaking microaneurysms, scattered punctate intraretinal hemorrhages, capillary nonperfusion, and possibly neovascularization. Thickening of the capillary basement membrane, one of the earliest histological changes in human diabetic retinopathy, occurs in experimental diabetes in cats and is in part inhibited by an aldose reductase inhibitor (Mansour et al. 1990).

The pathogenesis of diabetic retinopathy is complex, but retinal hypoxia appears to play a significant role (D'Amore 1994). Hypoxia stimulates increased production of vascular endothelial cell growth factor (VEGF¹), which in turn promotes neovascularization, a major cause of blindness in diabetes (Adamis et al. 1994; Mathews et al. 1997; Pe'er et al. 1996). The inner half of the retina of the cat becomes hypoxic early in diabetes, before capillary closure and non-perfusion become clinically apparent (Linsenmeier et al. 1998). This finding coincides with studies showing increased VEGF expression in diabetic humans with minimal or no signs of retinopathy (Amin et al. 1997; Luty et al. 1996; Mathews et al. 1997). Increased VEGF expression and neovascularization can also be stimulated by regional acidosis (Budzynski et al. 2005; D'Arcangelo et al. 2000; Holmes et al. 1999). Although the sample size was small and the hydrogen ion concentration varied between regions within the same retina, on average the inner retina of diabetic cats was more acidic than normal cats (Budzynski et al. 2005). Regional acidosis could be due in part to anaerobic glycolysis in a hypoxic environment. The retinal hypoxia noted in diabetic cats may result from capillary plugging or altered flow through microaneurysms (Schroder et al. 1991). Leukocyte activation, adhesion, and capillary plugging are increased in diabetic humans (Jackson et al. 1992) and rats (Schroder et al. 1991). Diabetic cats have enhanced superoxide radical production from activated polymorphonuclear leukocytes, which may contribute to microvascular injury and capillary plugging in the retina (Freedman and Hatchell 1992). In addition, abnormal blood rheology and leukocyte deformability have been documented in both diabetic humans (Pecsvary et al. 1994) and diabetic cats (Braun et al. 1996; Kelly et al. 1993). Thus, the domestic cat has played and will likely continue to play a valuable role in the study of the ocular manifestations of diabetes in humans.

Conclusion

The close parallels in clinical features, pathophysiology, pathology, and complications between FDM and human T2DM make FDM an excellent animal model of T2DM. Further study of FDM, therefore, may provide valuable insights into the pathogenesis of T2DM in humans.

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