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Review

Comparative aspects of diabetes mellitus in dogs and cats

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Abstract

Diabetes mellitus is a common disease in cats and dogs. Its incidence is increasing, possibly due to an increase in obesity in both species. Different types of diabetes have been identified in pet animals. The classification of diabetic dogs and cats is modeled after the human classification but especially in the diabetic dogs, many aspects are different. The diabetic cat, however, resembles type 2 diabetic human patients more closely. The clinical presentation, pathophysiology, and histologic findings are described for both dog and cat and possible etiological mechanisms are discussed.

Keywords: Insulin; Lipids; Glucose; Glucagon; Leptin

Diabetes mellitus is a very complex disease in people and equally so in the dog and cat. The etiology of diabetes in dogs and cats is not clear but is likely different in the two species.

1. Diabetes in the dog

Diabetes in the dog is mostly found in middle aged and older dogs (Marmor et al., 1982). Three main forms of diabetes occur in the dog. The classification is oriented towards the human diabetes classification, and it will be evident from the following discussion that there are many similarities, but also some key differences.

One form in dogs is similar to type 1 diabetes in people which is thought to be caused by autoimmune-mediated destruction of beta cells (Lendrum et al., 1976; Baekkeskov et al., 1982; Palmer et al., 1983). Dogs with this form of diabetes are prone to developing ketoacidosis and need insulin for survival. When beta cells are stimulated with glucose or glucagon in dogs with this form of diabetes, there is no increase in insulin (Mattheeuws et al., 1984) or C-peptide (Montgomery et al., 1996) suggesting that beta cells are either no longer present or have become completely unresponsive. Progressive destruction of beta cells is suggested by the observation of higher C-peptide concentrations in diabetic dogs that have been on insulin treatment for less than 6 months compared to those that have been treated for more than 1 year (Montgomery et al., 1996). In very young diabetic dogs (<1 year), insulin release in response to glucose has been shown to be erratic (Atkins et al., 1979) which may also indicate progressive destruction of beta cells.

Antibodies against several islet components (glutamic acid decarboxylase, tyrosine phosphatases or insulin) play an important role in the pathogenesis of type 1 diabetes in man. A majority of newly diagnosed type 1 diabetic people have antibodies. In addition, antibodies have been detected in the pre-diabetic period and can serve as a screening method to identify people at risk and design intervention therapy (Verge et al., 1996; Gorus et al., 1997). Antibodies were found against beta cells in 50% of the newly diagnosed diabetic dogs (Hoenig and Dawe, 1992) which would suggest an immune component in the etiology of the disease in dogs as well. The cellular target of the antibodies in diabetic dogs is unknown. In man and also in cattle (Taniyama et al., 1999) antibodies against glutamic acid decarboxylase or other islet components have been identified (Lendrum et al., 1976; Baekkeskov et al., 1982; Palmer et al., 1983; Baekkeskov et al., 1990). The canine antibodies were not directed against insulin, although the author has seen a few cases of insulin

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antibodies in newly diagnosed and untreated diabetic dogs (unpublished). Lymphocytic infiltration of islets which would support an auto-immune process in the destruction is detected infrequently in dogs. This is different from findings in type 1 diabetic people (Foulis and Stewart, 1984; Imagawa et al., 2001) and from insulin-dependent cattle (Taniyama et al., 1999) where lymphocytic infiltrations are commonly seen in acute cases. It is possible that lymphocytic infiltration occurs early in the disease process and is no longer present at the time of death of most dogs. However, even in the young diabetic dogs described by Atkins et al. (1979) and Atkins and Chin (1983), lymphocytic infiltration was not found. In 7 of 11 young diabetic dogs (<6 months) islets were not detectable while the other dogs had scant shrunken islets. Lymphocytes were found in only 3 dogs. They were located in interstitial fibrous tissue. It is likely that these very young dogs have a completely different etiology of diabetes than the majority of insulin-requiring dogs which develop the disease later in life. Antibodies against beta cells may also not be involved in the primary destruction process but may be a secondary response. A systematic experimental approach may be necessary to unravel the pathogenesis of diabetes in dogs. For example dogs could be screened for beta cell antibodies as well as alterations of glycosylated hemoglobin concentrations on a routine basis to provide information about the time course of the disease and establish risk factors. It may well be that the dog, similar to man, has a fairly long prodromal phase before diabetes becomes overt.

Few families of dogs with diabetes have been identified (Kramer et al., 1980); however, certain breeds, including Keeshounds, Alaskan Malamutes, Finnish Spitzes, Miniature Schnauzers, Miniature Poodles, and English Springer Spaniels, seem to be at increased risk to develop diabetes while others such as Boxers, German Shephard dogs, Cocker Spaniels and Collies seemed to be at decreased risk (Marmor et al., 1982). It is not known if some of these breeds might be at increased risk because they are prone to developing other endocrinopathies such as hyperadrenocorticism with insulin resistance caused by insulin-antagonistic hormones.

Histologically, several lesions may be found in insulin-dependent dogs. In about 30% of cases, the pancreatic islets are destroyed because of chronic relapsing pancreatitis and are replaced by fibrous tissue; in other cases, there is degeneration of the islets or no islets are found at all (Minkus et al., 1991; Gepts and Youssaint, 1967; Atkins et al., 1979). It is unknown if apoptotic processes are involved in the beta cell destruction of diabetic dogs as has been suggested recently in the pathogenesis of human beta cell damage (Kukreja and Maclaren, 1999; Eizirik and Darville, 2001; Mandrup-Poulsen, 2001). Vacuolization as well as glycogen deposits (hydropic degeneration) have also been seen in some dogs (Gepts and Youssaint, 1967), but it is possible that dogs with these kinds of lesions actually had a form similar to type 2 diabetes.

It is unknown if obesity is a risk factor for diabetes in the dog. It has been shown by Mattheeuws et al., (1982) that insulin secretion increases according to the degree of obesity. Dogs with approximately 40% body fat had normal glucose tolerance and insulin secretion; hyperinsulinemia was seen at higher degrees of obesity and only the group with the highest degree of obesity (approximately 75%) showed glucose intolerance. The same investigators (Mattheeuws et al., 1984) later identified 2 different populations of obese diabetic dogs: one with fasting hyperinsulinemia still able to respond to a glucose challenge with an increase in insulin secretion and another with markedly elevated fasting hyperinsulinemia but an inability to increase the secretion rate further in response to glucose. Comparing the blood glucose and insulin concentrations of dogs in these 2 studies during an intravenous glucose tolerance test (IVGTT), insulin secretion was lower in the obese diabetic group, despite a higher peak blood glucose than in the obese non-diabetic group. This decompensation is similar to what we have seen in cats (Hoenig et al., 2000a) and what has been described in people (Porte, 1991). In contrast to human type 2 diabetics, where a low first phase insulin release is an early marker of beta cell dysfunction (Gerich 2000, Gautier et al., 2001), it seems that insulin is released as rapidly in the obese dogs regardless of their glucose tolerance status (Mattheeuws et al., 1982; Kaiyala et al., 1999). It is evident from these studies that obesity in dogs leads to profound changes in glucose disposal and insulin secretion, however, a progression to overt diabetes has yet to be documented.

The third form of diabetes in dogs occurs in connection with endocrinopathies. The most common ones are hyperadrenocorticism (Peterson et al., 1981; Peterson, 1984; Hess et al., 2000) and acromegaly (Eigenmann et al., 1983; van Keulen et al., 1996). Acromegaly is especially prevalent in areas where bitches are not spayed at an early age because progestins may increase growth hormone release from the mammary gland (Selman et al., 1994; Kooistra et al., 2000). Often, but not always, diabetes secondary to other endocrinopathies is transient and the animal's glucose homeostasis becomes normal when the primary disease has been treated. Histologically, glycogen deposits or degranulation may be seen dependent on the stage of the disease. In a study of 60 dogs with untreated hyperadrenocorticism, 8 dogs had normal glucose and insulin concentrations, 24 dogs had euglycemia and hyperinsulinemia, 23 dogs had hyperglycemia and hyperinsulinemia, whereas 5 dogs had ketoacidotic diabetes and low but detectable insulin concentrations. After treatment of hyperadrenocorticism, glucose and insulin concentrations returned to normal in 20 dogs; however, insulin therapy was

required permanently in all 5 dogs with ketoacidotic diabetes. One might conclude from these findings that once animals decompensate and show hypoinsulinemia, beta cells are not able to recover. Because the time course of the primary disease was unknown, it is impossible to determine if the ketoacidotic dogs might have been exposed to high cortisol levels for longer and therefore their beta cells had a greater chance of becoming exhausted. Histopathological examinations were not available to document if these 5 dogs had more severe structural damage of their pancreas than the other dogs. In dogs in which diabetes was induced with growth hormone, high insulin concentrations, cytoplasmic glycogen storage in beta cells and beta cell degranulation was seen initially, followed by reduced insulin levels and beta cell atrophy with no sign of regranulation or neogenesis (Campbell et al., 1981).

2. Diabetes in the cat

Diabetes is a relatively common endocrinopathy in the cat. The incidence is approximately 0.5%. Several risk factors have been identified: age, obesity, neutering and gender (Panciera et al., 1990; Scarlett and Donoghue, 1998). Over 50% of diabetic cats were over 10 years old and age was identified as the most important single risk factor. Obesity is thought to increase the risk of developing diabetes 3 to 5 fold. Neutered cats have nearly twice the risk and male cats 1.5 times the risk of developing diabetes. Diabetes in young cats is extremely rare (Woods et al., 1994; Root et al., 1995)

It is thought that diabetic cats have primarily type 2 diabetes, based on the fact that most diabetic cats have islet amyloid (Yano et al., 1981) which has been called the hallmark of type 2 diabetes (Westermark and Wilander, 1978). Two other findings support the notion that type 1 diabetes is probably rare in cats: antibodies against beta cells have yet to be documented (Hoenig et al., 2000b) and lymphocytic infiltration of beta cells is extremely rare in diabetic cats (Hall et al., 1997). The authors of one study concluded that cats had type 1 and type 2 diabetes based on the fact that of the 30 cats that were examined 7 had increased insulin secretion after glucagon stimulation whereas 23 showed no increase in insulin (Kirk et al., 1993). It is questionable, however, if the secretion profile is a suitable marker for the type of diabetes, because it is well known that the beta cells in the later phases of type 2 diabetes become unresponsive, not only to glucose, but also to other stimuli (Mirel et al., 1980). The same authors found later (Nelson et al., 1999) that cats with transient diabetes mellitus showed no insulin response to glucagon while diabetic, yet, responded with insulin secretion when they were no longer diabetic. These observations do not support the use of secretion profiles when trying to characterize the type of diabetes.

It is unclear what role islet amyloid plays in the pathogenesis of cat diabetes because islet amyloid is not only seen in diabetic cats. Approximately 50% of non-diabetic aged cats have islet amyloid as well (Yano et al., 1981). An even larger number of amyloid positive non-diabetic aged cats was identified in a study from Australia (Lutz et al., 1994). Few studies have actually examined glucose tolerance, insulin secretion and islet pathology in the same cats. O'Brien et al. (1985) found that only 3 of 9 cats with impaired glucose tolerance and a significantly reduced first phase of insulin secretion had islet amyloid. Six diabetic cats had significantly decreased insulin release compared to healthy or glucose-intolerant cats in response to glucose during the first 45 min of the IVGTT; the same cats also had islet amyloid; however, there was no association between the severity of islet dysfunction and amyloid deposition. In another study by O'Brien et al. (1986), it was shown that 6 glucose-intolerant cats had a similar endocrine cell volume fraction as healthy cats. However both, A and B cell volume fractions were reduced or nonexistent in 6 overtly diabetic cats. This suggests that the initial defect in insulin secretion seen in glucose-intolerant cats occurs independently of changes in beta cell mass. Mandrup-Poulsen (2001) argued recently that the proper response to insulin-resistance should be beta cell hyperplasia. Therefore, the beta cell mass was inappropriately 'normal' in these cats. The study by O'Brien et al. (1986) also indicates that there is structural damage in islets during the progression from the glucose-intolerant to the overtly diabetic cat. Interestingly, in a recent study by Nelson et al. (1999) of cats with transient diabetes, amyloidosis (3 cats), vacuolar degeneration (3 cats), a decreased number of islets (4 cats) and a decreased number of insulin-staining cells per islet (2 cats) were found. Yet, despite all of these abnormalities, the cats returned to euglycemia.

Cats are very sensitive to the diabetogenic effect of some hormones. This was shown 6 decades ago by Lukens and Dohan (1942), and in recent work from our laboratory (Hoenig et al., 2000a). We administered growth hormone and dexamethasone to induce diabetes in partially pancreatectomized cats. It was interesting to see that insulin secretion became abnormal early in the course of treatment. A decrease in first phase and increase in second phase insulin secretion were the first changes that occurred, and were not associated with any change in glucose tolerance. A more drastic decrease in first phase and even more exaggerated second phase were associated with mild glucose intolerance. Later, first phase release disappeared completely and the total insulin secretion decreased by almost an order of magnitude. It was only then that fasting blood glucose became abnormally high and that severe glucose intol-

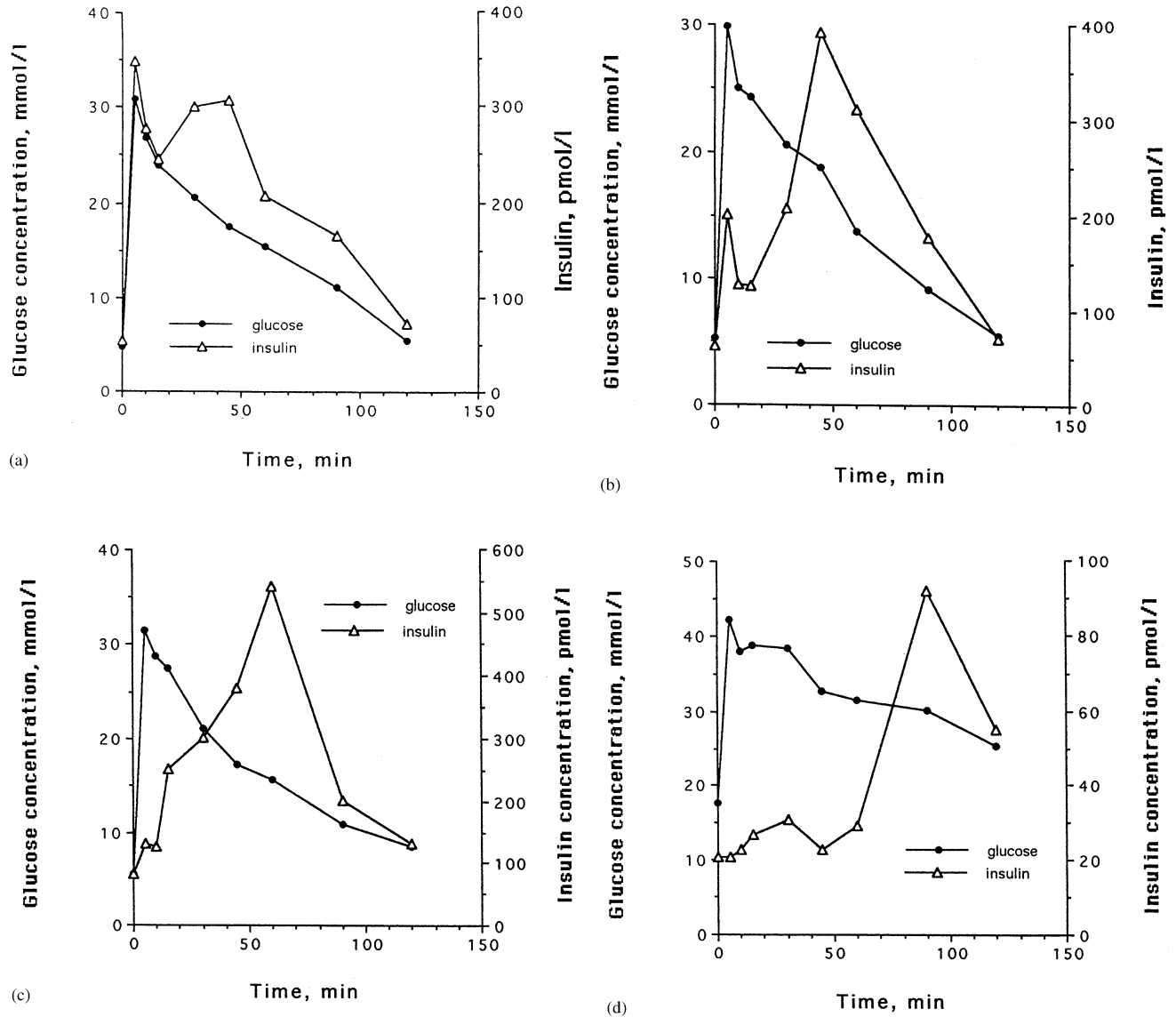

Fig. 1. (a) Mean plasma glucose and insulin concentrations in 8 cats after i.v. administration of glucose before partial pancreatectomy and treatment with growth hormone and dexamethasone; (b–d) Representative examples of sequential changes in glucose and insulin release in 1 cat during the diabetes induction with growth hormone and dexamethasone (Hoenig et al., 2000a).

erance was seen (Fig. 1). The insulin secretion in response to glucagon and tolbutamide were also markedly decreased in these cats. Islet histopathologic changes were not examined at that point in the study. The diabetic cats were then treated with either insulin or the sulfonylurea glipizide for $1\frac{1}{2}$ years. All cats on glipizide treatment, which leads to stimulation of insulin secretion, developed islet amyloid. This observation suggests that overstimulation of beta cells triggers amyloid formation. However, this study does not allow the conclusion that amyloid is causing the beta cell dysfunction.

In studies in obese cats, we have found that while insulin secretion is always abnormal when islets are stimulated with a glucose dose of 0.5 g/kg body weight or more, glucose tolerance may still be normal (Hoenig et al., 2002). In a large study comparing 34 obese (BMI 58.2±1.5, mean±SEM)) to 14 lean cats (BMI 41.7±1.3; mean±SEM), we found that on average, obese cats had glucose intolerance and abnormal insulin secretion when challenged with a large glucose load (1 g/kg body weight). The baseline glucose concentrations were also higher in obese cats than in lean cats, although still within the normal range (78±1 vs. 89±1; mean±SEM; $P < 0.025$; normal range: 3.9–6.7 mmol/l). Among this group of obese cats were 23 cats with normal glucose tolerance and 11 cats with glucose intolerance during the IVGTT. However, all obese cats demonstrated an abnormal insulin secretion pattern. The changes in the insulin secretion pattern are shown in Fig. 2. First phase

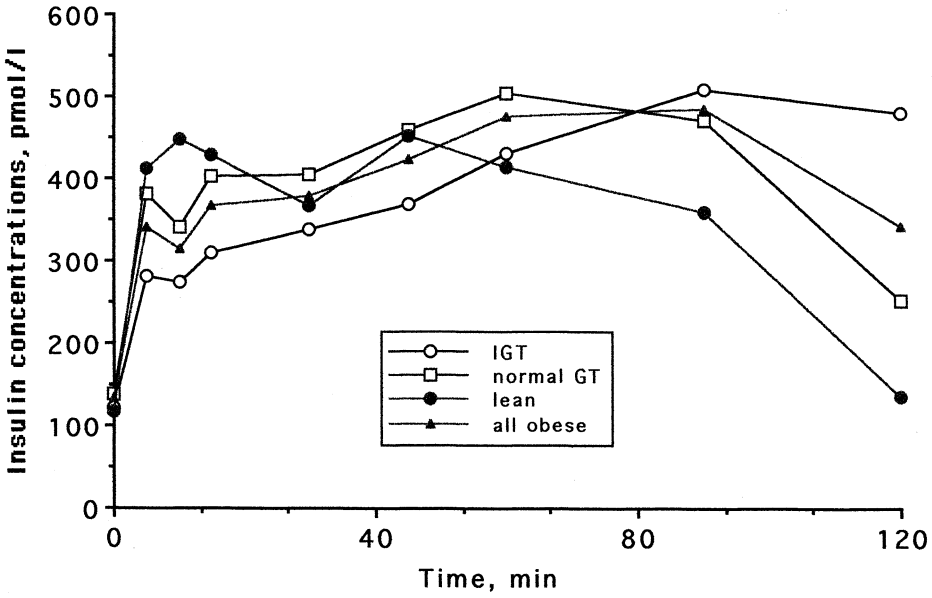

Fig. 2. Mean serum insulin concentrations in 14 lean and 34 obese cats. The 34 obese cats (all obese) were divided into 2 groups: cats with impaired glucose tolerance (IGT; $n = 11$) and cats with normal glucose tolerance (normal GT; $n = 23$).

insulin secretion was significantly lower ($P < 0.04$) and insulin secretion at 120 min was significantly higher in the lean compared to the obese cats; the 11 glucose-intolerant obese cats had the most marked changes compared to the glucose-tolerant obese ($P < 0.005$) and to the lean cats ($P < 0.003$). One can conclude from this study that the insulin secretory defect occurs very early in the process, before changes in glucose tolerance are obvious and is not due to changes in glucose concentrations. This is supported by the fact that glycosylated hemoglobin concentrations were not different between lean and obese cats (1.72 ± 0.05 in lean cats; 1.75 ± 0.04 in obese cats; mean $\pm$ SEM). The total area under the curve for insulin was not significantly different between the lean and obese cats, regardless of their glucose tolerance status (Fig. 3). We conclude that glucose-intolerant cats have relative insulin deficiency, because they are not able to increase insulin output to overcome glucose intolerance.

It is unclear what alters insulin secretion in obese cats and what factors might be involved causing the progression to diabetes. One hypothesis might be that the hyperstimulation in the insulin resistant state leads to amyloidosis as we have shown in the growth hormone/dexamethasone model (Hoenig et al., 2000a). Amyloid would then replace functional beta cell mass and the cats

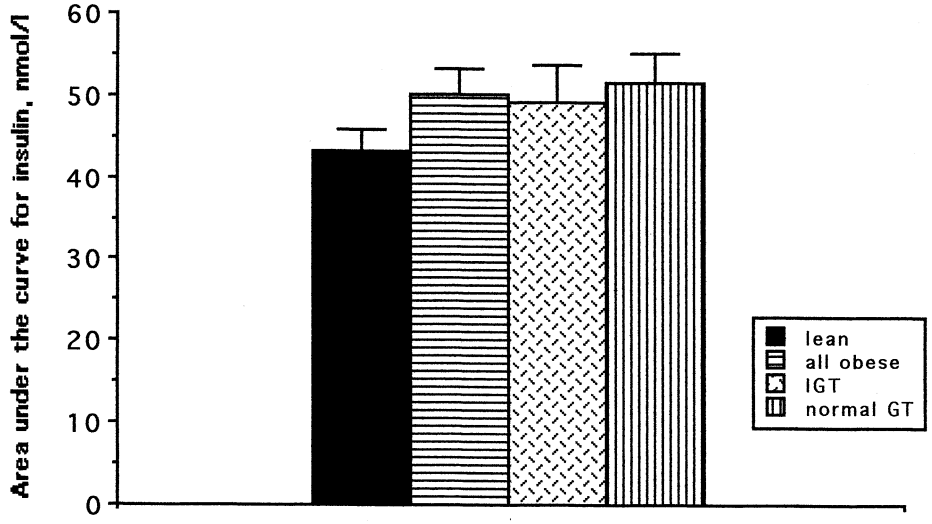

Fig. 3. Area under the curve for insulin (nmol/l; mean $\pm$ SEM) in 14 lean and 34 obese cats (all obese). The 34 obese cats were divided into 2 groups: cats with impaired glucose tolerance (IGT; $n = 11$) and cats with normal glucose tolerance (normal GT; $n = 23$). There was no statistically significant difference among the groups.

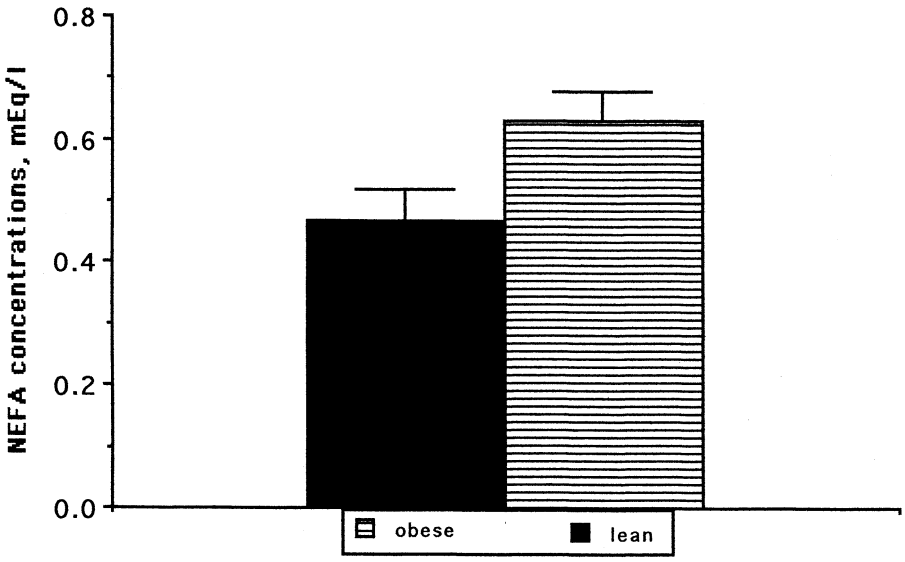

Fig. 4. Serum non-esterfied fatty acid (NEFA) concentrations in 14 lean and 34 obese cats ($P = 0.03$)

would no longer be able to overcome the insulin resistance by increasing insulin output. There is no study that has examined islet histopathology at various stages of the progression towards diabetes in the cat. It is known, however, that not all glucose-intolerant cats have islet amyloid, and that the degree of amyloidosis is not well correlated with functional defects. Beta cell dysfunction appears to be more important in the pathogenesis of diabetes in the cat than beta cell loss due to amyloid. It has recently also been shown in people that beta cell mass was preserved in 82% of type 2 diabetics and beta cell insulin reserve and biosynthetic capability was maintained, suggesting that type 2 diabetes is not due to a significant beta cell loss (Guiot et al., 2001; Sempoux et al., 2001).

It is also conceivable that the hypersecretion that occurs during the maintenance phase of insulin release leads to exhaustion of beta cells over time. This is likely a very slow process because we have followed obese cats for 2 years and have not seen a change in glycosylated hemoglobin concentrations. In fact, none of the 34 obese cats had significant changes in their glycosylated hemoglobin values over 2 years, and all values were well within the normal range (0.8–1.9%). In a retrospective survey in our hospital, 5 obese cats were followed for 6–12 years and did not develop diabetes. Another 3 cats were diagnosed with obesity and developed diabetes 4–11 years later. In another 4 cats with obesity of unknown duration, diabetes developed 12–18 months after initial presentation.

There has been evidence that fatty acids and triglycerides may play a role in the deterioration of beta cell function, and may be involved in the progression from the obese to the diabetic state. It has been well known

Fig. 5. Serum triglyceride concentrations in 14 lean and 34 obese cats ($P = 0.0061$)

for almost 4 decades that an interaction exists between glucose and fat metabolism (Randle et al., 1963). Glucose inhibits fatty acid oxidation and fatty acids inhibit glucose oxidation (glucose fatty acid cycle). Glucose must be metabolized in order to cause insulin secretion. Therefore, decreased glucose metabolism due to increased fatty acid concentrations might explain the lowering of the early phase insulin secretion in obese patients. Comparing 14 lean and 34 obese cats, we found that the obese cats had increased baseline non-esterified NEFA concentrations as well as triglyceride concentrations (Figs. 4 and 5). However, there was no significant difference in NEFA or triglyceride concentrations between glucose-intolerant and glucose-tolerant obese cats. Therefore, increased baseline NEFA and triglyceride concentrations may be important causative factors in the defective insulin secretion. Their involvement in the progression to diabetes is, as yet, unclear. Triglyceride deposits in beta cells have been shown in obese Zucker rats and have been implicated as a cause for beta cell apoptosis. An increase in NEFA also has been shown to cause apoptosis (Shimabukuro et al. 1998). While fat deposits in beta cells are not a feature of diabetic cats, it is possible that cats have increased beta cell uptake of fatty acids which may lead to apoptosis as has been shown in rats (Shimabukuro et al. 1998).

It is interesting to note that NEFA concentrations suppress more in the obese than the lean cats during the IVGTT, suggesting either increased fatty acid oxidation or an increase in fat deposition in the obese cat. It is especially remarkable that this finding was seen in the glucose-intolerant group of obese cats as well, which indicates that insulin resistance may be substrate- and possibly tissue-specific. An increase in fatty acid uptake and an increase in lipoprotein lipase activity has recently been shown in obese Zucker rats. The changes were due to hyperinsulinemia and were not seen when insulin secretion was inhibited with diazoxide (Berk et al., 1997; Standridge et al., 2000). It is possible that a similar phenomenon occurs in cats.

Other hormones may have a role in the pathogenesis of obesity and diabetes. Leptin has recently been shown to be important for fatty acid homeostasis (Unger et al., 1999). Leptin resistance may lead to fat deposits in non-adipose tissue causing dysfunction. Leptin concentrations increase in obese cats correlating highly with the degree of obesity (Hoenig, 2000a). It is assumed that obese cats have leptin resistance because the increase in leptin is not associated with a decrease in food intake. The importance of this finding is unknown at this time.

Hyperglucagonemia is a well known feature of obesity and type 2 diabetes in other species and is thought to be secondary to the reduction of insulin action on alpha cells (Hamaguchi et al., 1991). Glucagon concentrations are significantly higher in obese than in lean cats and may be important in the progression from obesity to diabetes as glucagon increases insulin resistance and may hasten exhaustion of beta cells.

We are just beginning to unravel cellular mechanisms involved in the pathogenesis of diabetes not only in pet animals but also in people. The problems we are facing in veterinary medicine are similar to those in human medicine, i.e. our pet population is becoming more sedentary and more obese. Food supply is ample. The incidence of obesity is increasing, and with it, the incidence of diabetes.

An interesting observation recently has been that a high protein diet reduces the insulin requirement of diabetic cats (Frank et al., 2001, Bennett et al., 2001). Cats are strict carnivores and, as such, the diet of feral cats consists of a large amount of protein and fat, but very little carbohydrate (Bradshaw et al., 1996). Yet, many commercial pet food types that are available for cats have large amounts of carbohydrates. We have shown that high carbohydrate diets decrease insulin sensitivity (Hoenig et al., 2000b), and cause hyperinsulinemia compared to a diet high in protein. The clinical effect of the high protein diet has been encouraging, and in some diabetic cats insulin treatment is no longer required (Frank et al., 2001; Bennett et al., 2001). While the long-term effect of this diet needs to be investigated, a lesson of nature may be learned from it.

3. Conclusion

Diabetes in animals shares many similarities to diabetes in man. It is a multifaceted disease and remains a humbling challenge for the clinician and the researcher.

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