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SYMPOSIUM

The Cat as a Model for Human Obesity and Diabetes

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Abstract

Obesity is the most common nutritional disorder of cats and is a risk factor for diabetes. Similar to developments in obese people, obese cats show peripheral tissue insulin resistance and may demonstrate glucose intolerance when challenged with pharmacological amounts of glucose. However, they compensate well for the insulin resistance and do not show elevated glucose concentrations when monitored during their regular daily routine, including postprandial periods. This is possible because obese cats in the fasted and postprandial state are able to maintain hepatic insulin sensitivity and decrease endogenous glucose production, which allows them to maintain normoglycemia. Also dissimilar to what is seen in many obese humans, cats do not develop atherosclerosis and clinical hypertension. The time course for progression to overt diabetes of obese cats is unknown. One might speculate that diabetes develops when the liver finally becomes insulin resistant and/or insulin secretion becomes too low to overcome increased glucose production. In addition, amyloid, demonstrated to be deposited in islet of chronically obese cats, may contribute to a reduction in insulin secretion by reducing functional β-cell mass.

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Introduction

Obesity is a risk factor for diabetes in both humans and cats.[1,2] Obesity is well defined in people. In cats, obesity can be assessed subjectively using the body scoring system developed by Laflamme.[3] Objective ways to judge obesity in cats also exist but are not usually perfomed in clinical practice. Body mass index (BMI) is well known from human medicine, where it is used ubiquitously to assess adiposity. It can be calculated in cats according to the following formula:[4]

$$\text{BMI} = \text{body weight (kg)} / [\text{body length (m)} \times \text{height (m)}],$$

where height is the distance from the point of the shoulder through the point of the elbow to the proximal boundary of the metacarpal pad and length is the distance from the point of the shoulder to the tuber ischium. The feline body mass index is calculated according to the following formula:

$$\text{Percentage body fat} = [(\text{rib cage} / 0.7062) - \text{LIM} / 0.9156] - \text{LIM},$$

where rib cage is the rib cage circumference in centimeters and LIM is the length of the lower leg from the middle

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Abbreviations: (BMI) body mass index, (DEXA) dual energy X-ray absorptiometry, (EGP) endogenous glucose production, (EHC) euglycemic hyperinsulinemic clamp, (HDL) high-density lipoprotein, (HOMA) homeostatic model assessment, (IVGTT) intravenous glucose tolerance test, (LDL) low-density lipoprotein, (VLDL) very-low-density lipoprotein

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of the patella to the dorsal tip of the calcaneal process in centimeters.[5] Obesity also can be assessed by measuring the girth circumference immediately caudal to the last rib.[6] Both girth and BMI measurements do not need any specialized equipment. Highly sophisticated evaluations of adiposity include dual energy X-ray absorptiometry (DEXA) and magnetic resonance imaging.[7,8] The latter allows the exact localization of fat depots in the body, which is not possible with DEXA. We have found that BMI and girth correlate well with DEXA results and are excellent objective markers of adiposity that could be used by clinicians. When cats become obese, both abdominal subcutaneous and visceral fat mass increase to the same extent,[7] which contrasts with human subjects, where obesity is usually associated with a larger increase in abdominal visceral than abdominal subcutaneous obesity.[9] There are no published data on veterinary standards for lean, overweight, or obese cats for any of the objective measurements to date. However, results of objective obesity measurements have been described in lean and obese cats, which have been used in research projects (e.g., Reference 7); they were mostly domestic shorthair cats.

The prevalence of feline obesity seems to be increasing and so is the prevalence of diabetes. Obesity is now seen in approximately 35% to 50% of cats.[2,10] Feline diabetes has increased from 0.08% to 1.2 % in three decades in the United States.[11] A prevalence of 0.4% was recorded in the United Kingdom.[12] Diabetes is usually seen in older cats implying that pathophysiological mechanisms involved in the progression from obesity to diabetes may require years to develop. Obviously, not all obese cats become diabetic and, similar to other species, genetic, environmental, and metabolic factors may significantly influence the response to long-term obesity.

Glucose homeostasis depends on β-cell function, endogenous glucose production (EGP) by the liver, and glucose utilization in peripheral tissues, primarily muscle. The hallmark of diabetes in people is hyperglycemia, which develops when peripheral tissues and the liver become resistant to the effect of insulin, when EGP increases, and when insulin secretion becomes abnormal.[13] It would be advantageous to find markers that forebode impending diabetes before overt hyperglycemia is obvious. Pursuant to this goal, the obese cat has been used in several studies as a model to elucidate factors contributing to progression from obesity to diabetes.

Insulin Sensitivity/Resistance Is Tissue Specific

Peripheral insulin resistance usually describes the loss of insulin action in muscle and adipose tissue. Obese cats have increased amounts of intramyocellular and extramyocellular fat,[7] which has been associated in people with a loss of insulin sensitivity.[14] The higher amount of fat in muscle is due to a shift in the expression and activity of lipoprotein lipase. This enzyme responsible for uptake of fatty acids into tissues is lower in adipose tissue but higher in muscle tissue, leading to a partitioning of fatty acids to muscle.[15] It has also been shown that tumor necrosis factor-α expression is higher in adipose tissue in obese cats,[15] and this cytokine has been purported to downregulate lipoprotein lipase.[16,17] The loss of insulin sensitivity in muscle tissue is not always accompanied by a loss of insulin sensitivity in fat tissue. During the euglycemic hyperinsulinemic clamp (EHC), nonesterified fatty acids were suppressed to a significantly higher degree in cats on a high-carbohydrate diet but not in those on a high-protein diet, indicating that insulin sensitivity is regulated in a tissue-specific way and can be influenced by diet.[7] The greater insulin sensitivity of adipose tissue in that study, however, did not lead to a greater fat deposition, likely because the high insulin concentrations achieved during the clamp exceed the physiological insulin response after regular food intake. It is also possible that diet influenced nonesterified fatty acid metabolism independently of the action of insulin. A similar suppression of nonesterified fatty acids has also been seen during the intravenous glucose tolerance test (IVGTT).[18]

As stated earlier, glucose homeostasis not only depends on peripheral glucose uptake, but also on the EGP by the liver. In order to evaluate glucose output by the liver, a noninvasive approach employing nuclear magnetic resonance spectroscopy was used. This method has been used in humans,[19] rats,[20] and mice[21] to investigate metabolic pathways in glucose production using a triple tracer method. Applying this method, it is possible to detect key steps in glucose metabolism (glucose turnover and gluconeogenic fluxes) with a single blood sample using stable, nonradioactive isotopes [^2H_2O, (U-$^{13}C_3$) propionate, and (3,4-$^{13}C_2$) glucose]. We utilized this methodology to study the metabolic pathways involved in glucose metabolism in lean and obese neutered male and female cats. We hypothesized that the insulin resistance of obese cats will be reflected in the activity

of different metabolic pathways leading to hepatic glucose production. However, we found that obese cats compensate well for the peripheral insulin resistance by maintaining insulin sensitivity in the liver, allowing them to decrease EGP and to maintain normal blood glucose concentrations not only in the fasted, but also in the postprandial state.[22,23] This was partially accomplished through pyruvate cycling. This futile cycle was higher in obese cats. Gluconeogenesis was the main contributor to EGP in fasted and postprandial cats. This was expected. It was, however, interesting that glycogenolysis accounted for approximately 35% of fluxes contributing to EGP in fasted cats and approximately 40% in postprandial cats. With the exception of one study,[24] it has always been thought that cats do not produce much glycogen,[25,26] however, this is clearly not the case. The hepatic glycogen content of 24 h fasted cats is similar to those found in people after a similar fast.[27] Therefore, both gluconeogenic and glycogenolytic contributions to glucose production in the liver of cats (lean and obese) are similar to what has been documented in people. Histologically, glycogen seems to be abundant in the liver, and biochemical measurements show that, in 24 h fasted cats, approximately 5% of liver weight is from glycogen.[23]

Changes in Insulin Secretion during the Development of Insulin Resistance and Diabetes

Only one study has followed the insulin secretory pattern in response to an intravenous glucose load during the development of diabetes in cats. It shows that there is a distinct change in the secretory pattern of insulin, and one can distinguish different phases in the progression toward diabetes.[28] Healthy lean cats have a biphasic insulin secretion pattern when stimulated with 1 g of glucose per kilogram body weight during an IVGTT. The glucose and insulin concentrations return to baseline at 120 min with the high dose of glucose (**Figure 1**). With the development of insulin resistance, there are changes in insulin secretion. Plasma insulin concentrations increase to a level that is high enough to allow the maintenance of normal glucose tolerance. With continued insulin resistance, the second phase of insulin secretion becomes even more prominent, and there is approximately 50% more insulin secreted during that phase compared with when the cats were insulin sensitive. Glucose clearance is delayed in those cats; however, baseline glucose is still normal (**Figure 2**). As insulin resistance continues and progresses, glucose clearance becomes abnormal, even in the fasted basal state, and insulin secretion becomes erratic and much lower than in normal or insulin-resistant cats. These cats are now diabetic (**Figure 3**). What leads to the deterioration of insulin secretion is clearly not glucose toxicity, because

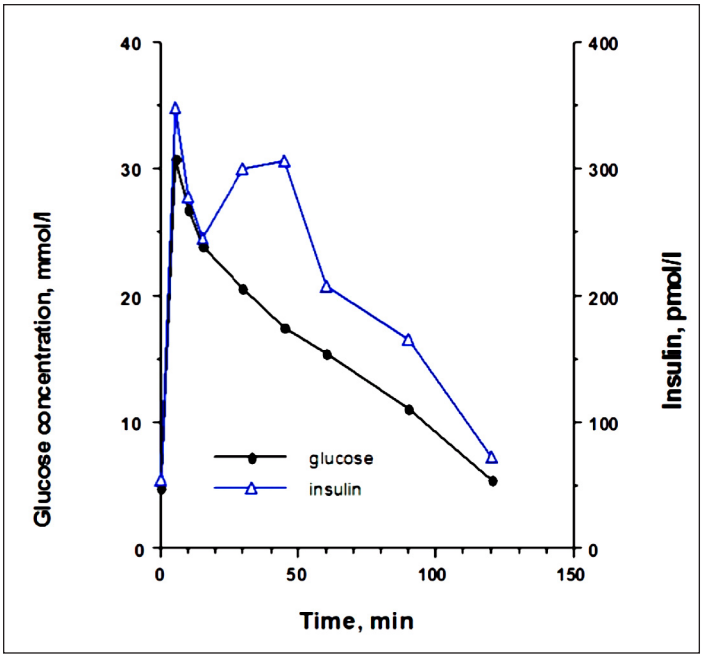

Figure 1. Plasma glucose and insulin concentrations in eight cats after intravenous administration of glucose before partial pancreatectomy and treatment with growth hormone and dexamethasone (mean ± standard deviation). Reprinted with permission from *American Journal of Pathology*.[28]

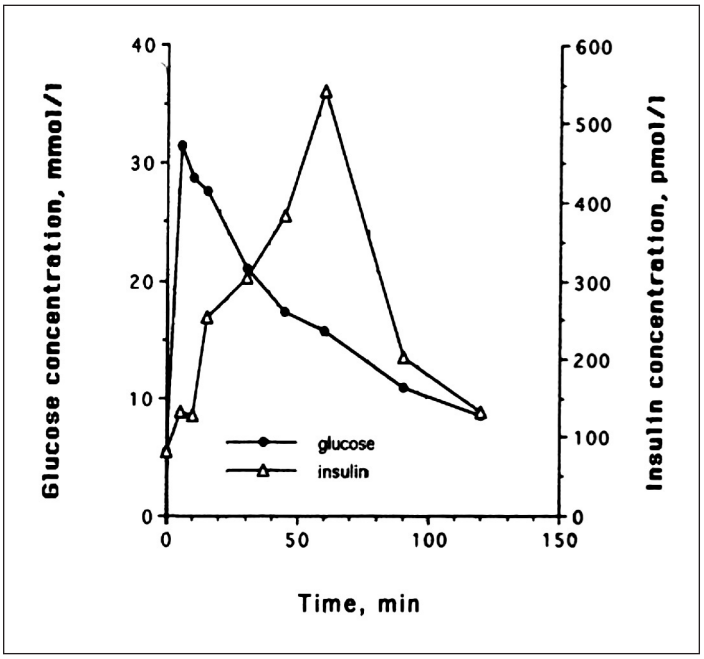

Figure 2. Representative example of changes in glucose and insulin release in one cat during the diabetes induction with growth hormone and dexamethasone. After 2 months, delayed glucose clearance is seen, but baseline glucose concentrations are still normal. Reprinted with permission from *American Journal of Pathology*.[28]

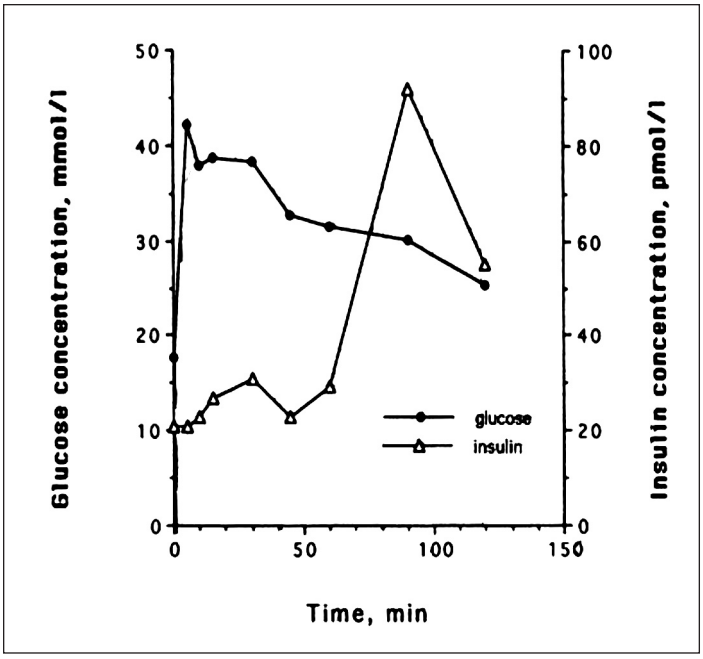

Figure 3. Representative example of changes in glucose and insulin release in one cat during the diabetes induction with growth hormone and dexamethasone. As insulin resistance continues and progresses, glucose clearance becomes abnormal, even in the fasted basal state. Insulin secretion becomes erratic and is much lower than in normal or insulin-resistant cats. These cats are now diabetic. Reprinted with permission from American Journal of Pathology.[28]

insulin secretion is abnormal long before glucose levels rise in the fasted state and long before glucose clearance becomes abnormal. In addition, one needs to consider that glucose concentrations in cats during their daily routine, including food intake, do not reach the blood glucose levels that are seen with the pharmacological amounts of glucose that are administered in an IVGTT, as described earlier.

It is known that hypersecretion of insulin leads to hypersecretion of the hormone islet amyloid polypeptide, also called amylin (for review, see Reference 29). Many obese cats are hyperinsulinemic for many years and also show hyperamylinemia.[30,31] In one study, we found that long-term obese old cats had fewer, but larger, pancreatic islets, often with pronounced amyloid deposition within the pancreatic islets.[32] Fasting glucose concentrations were still normal in these cats. It has previously been shown that cats with impaired glucose tolerance have higher amyloid depositions;[33,34] however, no change was seen in the insulin content of β cells in those cats as determined by immunohistochemistry. Therefore, with time, long-term hypersecretion of insulin and amylin resulting from insulin resistance leads to amyloid deposition and β-cell loss, likely through apoptosis. It is not known what amount of amyloid must be present before insulin secretion becomes low and erratic. It is also known that not all cats with diabetes have pancreatic amyloid and that diabetes can be transient despite the presence of amyloid. Nelson and colleagues[34] have shown that 3 of 5 cats with transient diabetes had islet amyloid, whereas 2 of 5 age-matched control cats also had islet amyloid, although to a much lesser degree.

One might therefore speculate that progression from the obese to the diabetic state is due to the following: (1) a decrease in insulin secretion either because of islet amyloid leading to islet destruction or some other pathophysiological mechanism leading to β-cell failure, the hypoinsulinemia then would lead to increased EGP production by the liver because the suppressive effect of insulin is no longer present, or (2) EGP increases because of hepatic insulin resistance overwhelming the β-cell secretory machinery and leading to β-cell exhaustion. A combination of both events could also occur simultaneously. The higher blood glucose leads to toxic changes of the β cells, which already have been described over 60 years ago by Dohan and Lukens.[35]

Evaluating Insulin Sensitivity and Glucose Tolerance

Several studies have reported that obese cats show insulin resistance of peripheral tissues, although only one group of investigators has used the EHC in obese cats, which is considered the gold standard method for assessing insulin resistance in people.[12,36,37] The EHC is a method that measures the amount of glucose necessary to compensate for a constant level of hyperinsulinemia without causing hypoglycemia. This experimental procedure was first introduced to feline research by Petrus and coworkers.[38] This test does not rely on a feline-specific insulin assay, because it is regular recombinant human insulin, which is infused in high amounts during the test. An insulin-sensitive cat needs more glucose than an insulin-resistant cat to maintain euglycemia. Using this method, it was documented that obese cats had insulin resistance and lower glucose effectiveness, i.e., glucose uptake that is insulin independent.[7,37] It had also previously been demonstrated that the development of feline obesity is associated with a decrease in the insulin-dependent glucose transporter expression, glucose transporter-4, in muscle and subcutaneous fat, whereas the insulin-independent glucose transporter, glucose transporter-1, expression is not altered.[39]

Other tests have been used in cats to evaluate insulin sensitivity. The response to a fixed and small amount of insulin (0.1 U/kg) has been examined.[40,41] Unfortunately, this amount of insulin leads to hypoglycemia. It has been cautioned by Brehm and associates[42] that hypoglycemia and the subsequent release of insulin-antagonistic hormones will lead to overestimation of insulin resistance.

The frequently sampled IVGTT combined with an insulin injection at 20 min (called modified frequently sampled IVGTT) has been compared with the EHC in cats[36,40] and was found to overestimate insulin resistance, and results were highly variable.[36] Results from this test are analyzed with minimal model analysis. In people, the analysis is often performed using a computer program, the MinMod Millennium.[43] The utility of this program for the accurate analysis of insulin sensitivity in cats has not been critically evaluated. One of the protocols, which has been described in cats,[44] may lead to hypoglycemia in non-diabetic cats. Hypoglycemia, however, as stated earlier, needs to be avoided because it has been shown that the counterregulatory reflex associated with hypoglycemia leads to an incorrect estimation of insulin sensitivity.[42,45] The IVGTT without insulin administration has been frequently performed in cats to assess primarily glucose disposal and occasionally to assess insulin sensitivity.[40,41,46–49] This is a dynamic test where glucose is injected intravenously as a bolus and blood samples are taken at various intervals usually for 120 min or longer. Depending on the dose of glucose that is administered, glucose and insulin concentrations return to baseline levels between 60 and 90 min (0.5 g/kg body weight) or 90 and 120 min (1 g/kg body weight) in lean cats, whereas insulin concentrations remain higher in obese cats throughout the test, but glucose clearance is usually still normal.[41,47] Because it is a dynamic test, it is better suited to examine the insulin secretory capacity of the β cells, especially during the earlier time points, rather than as a measure of insulin sensitivity, and it is difficult to distinguish secretion from action with this testing method unless specific mathematical methods are employed for the analysis.

Other simpler and less work-intensive methods to assess insulin sensitivity are available in human medicine. The first was the homeostatic model assessment (HOMA),[50] and a later method is the quantitative insulin sensitivity check.[51] Both methods employ fasting glucose and insulin concentrations to calculate insulin sensitivity, and in people, both correlate reasonably with the results of clamping studies. These tests are based on the assumption that higher insulin concentrations are needed to maintain basal glucose concentrations in the normal range in a person with insulin resistance. However, it has been pointed out that fasting insulin concentrations not only indicate insulin sensitivity, but also reflect insulin secretion as well as metabolic clearance of the hormone. Therefore, they do not accurately reflect insulin sensitivity in patients with β-cell dysfunction.[52] The HOMA has not been validated for use in cats or other animals, and according to Wallace and associates,[53] "such use violates the assumptions of the model." It has also been shown in the dog that HOMA of insulin resistance is inadequate to reflect changes in insulin sensitivity, and the authors concluded that it was necessary to use other, accurate indices to measure changes in insulin sensitivity.[54]

Lastly, the hyperglycemic clamp has been used to evaluate insulin sensitivity in cats.[55] This method is usually employed to examine the β-cell secretory response to glucose in people (β-cell sensitivity). There, it has also been shown to correlate well with other indices of insulin sensitivity.[56] A comparison of this method with the EHC has not been conducted in cats.

It is obvious that much more work is needed to validate many of the tests that are employed in human medicine for use in cats, and any conclusions based on results from tests that have not been validated for cats need to be examined with caution. A confounding problem for assessment of insulin sensitivity is the lack of a specific and sensitive feline insulin assay to measure endogenous insulin concentrations.

A variety of questions arise from our current state of knowledge about assessment of the progression toward diabetes in cats: What do we learn from any of these tests? Can they be used to predict progression from obesity to diabetes in cats? Does peripheral insulin resistance predict the timeline for the development of overt diabetes? Would progression in cats not be indicated by an increase in fasting blood glucose concentrations and/or an increase in postprandial glucose concentrations similar to the diagnostic threshold for type 2 diabetes in people? Why are veterinarians not using fasting glucose concentrations or oral glucose tolerance tests as indicators for progression in cats?

In human medicine, fasting blood glucose concentrations repeatedly higher than 126 mg/dl are diagnostic for diabetes mellitus. In addition, the oral glucose tolerance test is one of the most frequently used tests to evaluate a person's ability to dispose of a glucose load in a timely fashion. Interpretation of this test is based on

the assumption that a healthy adult person should be able to metabolize a standard amount of glucose taken orally within a defined period of time. This is a more physiological assessment than, for example, the IVGTT, because glucose is normally presented to the body by ingestion, and the same mechanisms, including the incretin response, are initiated, which are responsible for the maintenance of glucose concentrations after consumption of a meal.[57] Diabetes is diagnosed if a person has a blood glucose over 200 mg/dl 2 h after the ingestion of glucose.

Evaluating fasting glucose concentrations in cats is problematic. Many client-owned cats have a high incidence of stress hyperglycemia[58] regardless of body condition. This is likely different in colony cats that have been well adjusted to blood sampling. It is known from those research populations that cats do not show an increase in fasting blood glucose concentrations even with long-term obesity or drug-induced insulin resistance[22,28] and do not show a change in fasting blood glucose until insulin secretion becomes low and erratic.[28] Results from the oral glucose tolerance test have been reported in experimental cats.[59] Unfortunately, the response to glucose was variable, and a clear distinction between individual lean and obese cats was not possible. High variability of the results has also been described in dogs.[60] This test, therefore, cannot be recommended as a routine test to examine the risk of developing diabetes in individual cats as it is used in people.

A different approach has been recently taken to see if obese cats with documented peripheral insulin resistance based on EHC and IVGTT showed a difference in glucose concentrations when monitored over several days, including the postprandial periods. Measurement of blood glucose concentrations using a laboratory reference method and a handheld glucometer and evaluation of interstitial glucose concentrations using a continuous glucose monitoring system were performed for 7 days during the normal daily routine of six lean and eight long-term obese old cats who had documented peripheral insulin resistance for many years. It was found that there was no difference in glucose concentrations between lean and 7 of 8 long-term obese and insulin-resistant cats over this 7-day recording period. Only 1 of 8 cats could be identified as prediabetic (blood glucose values were approximately 25% higher than in the lean and 7 of 8 obese cats).[61] This indicates that tests used to assess peripheral insulin resistance or IVGTTs are of little value in the prediction of daily glucose homeostasis in cats, even in cats that have been severely obese and insulin-resistant for several years.

Do Obese Cats Develop the Metabolic Syndrome?

Metabolic syndrome is the name for a cluster of risk factors for atherosclerosis, coronary artery disease, stroke, and diabetes mellitus.[13] Increased weight and insulin resistance are probably the most important risk factors in people.[62] They are associated with alterations in several hormones and lipoproteins, including elevated cholesterol, triglycerides, and apolipoprotein B concentrations, as well as higher very-low-density lipoprotein (VLDL), higher low-density lipoprotein (LDL), and lower high-density lipoprotein (HDL) cholesterol levels.[62] It has been shown that the number of lipoprotein particles and their size that determine risk for disease.[63–65] In people, large VLDL and small LDL and HDL particles are associated with insulin resistance and associated cardiovascular problems. In cats, increased weight and insulin resistance are also associated with lipid changes similar to what has been reported in humans. Obese cats showed an increase in nonesterified fatty acids, VLDL, and plasma triglycerides, primarily originating from VLDL. In fact, the increase in triglycerides in the VLDL fraction was, on average, 500% higher in obese cats than in lean controls. Overproduction of VLDL has been associated with decreased expression of peroxisome proliferator-activated receptor α. Peroxisome proliferator-activated receptor α is involved in adipocyte mitochondrial biogenesis and the upregulation of genes involved in fatty acid oxidation[66] and is low in obese cats.[67]

Despite high VLDL concentrations, obese cats had no change in baseline LDL concentrations, suggesting that VLDL was metabolized rapidly to LDL, and LDL clearance was increased to maintain normal levels. The over-production of VLDL in cats was associated with an increase in the VLDL particle number. The particles were of large and medium size, which, in people, has been associated with cardiovascular disease.[63] Especially large triglyceride-enriched VLDL can bind to LDL receptors and lead to the formation of cholesterol-rich foam cells in people;[68,69] however, this has not been documented in cats. Large VLDL particles are linked with small LDL and HDL particles, and it has been suggested that the high triglyceride contents of large VLDL is the major predictor of LDL size in type 2 diabetes patients. Increased levels of small, dense LDL have been shown to be strongly associated with coronary artery disease risk in people.[70,71] Very small and medium small LDL particles were almost three-fold increased in obese cats, whereas only large particles were detected in lean cats.[72] Small HDL particles have also been associated with

cardiovascular disease.[73] As in obese people, small particle concentrations were significantly higher in obese cats.[72] Despite all these changes in lipoprotein concentrations, particle number and size, atherosclerosis, coronary artery disease, and stroke or clinical hypertension have not been described in obese or diabetic cats.

Hormonal Changes Associated with Obesity in Cats

The changes in metabolism that are seen in obese cats may, in part, be caused by alterations of hormones involved in metabolic regulation. Adiponectin[7,74] and leptin[7,75,76] have been studied in cats in more detail. Adiponectin is a hormone that is secreted by adipocytes. This hormone has beneficial effects on glucose and lipid metabolism.[77] It stimulates fatty acid oxidation and suppresses hepatic gluconeogenesis. It inhibits inflammatory responses that, in people, have been associated with insulin resistance and the metabolic syndrome. In obese cats, adiponectin levels are inversely related to the degree of adiposity, and weight loss leads to an increase in adiponectin[7] to levels that are not different from those seen in lean cats.

Leptin is also secreted from fat cells. It acts by binding to specific receptors in the hypothalamus, where it alters the expression of several neuropeptides involved in the regulation of neuroendocrine function, energy intake, and expenditure.[78] Obese cats are leptin-resistant, indicated by the fact that leptin concentrations are several-fold higher in obese compared with lean cats without causing the appropriate physiological response.[7] Fortunately, with weight loss, leptin levels in obese cats normalize, and leptin is therefore a good indicator of fat mass.[7,75] We have recently shown that both leptin and insulin are higher in old lean cats compared with young lean cats, despite similar body fat mass, suggesting development of both insulin and leptin resistance with aging. Thyroid hormone resistance has been postulated by the observation of an increase in free[79] and, sometimes, total thyroxine[22] in obese cats.

Conclusions

Obese cats have many similarities and dissimilarities to obese people. The major dissimilarity is the fact that cats do not develop atherosclerosis and clinical hypertension. The main similarity is insulin resistance. However, cats seem to compensate well for the insulin resistance by lowering their glucose output from the liver and are able to maintain normal glucose concentrations, even postprandial, for many years, despite peripheral insulin resistance. Measurement of insulin resistance alone, therefore, will not allow us to predict progression to diabetes, neither will glucose tolerance testing with pharmacological amounts of glucose. Only an increase in glucose concentrations during their daily routine will indicate progression. Measures of long-term glucose control might, therefore, be better indicators if it can be shown that the progression from the insulin resistant/glucose tolerant state to overtly diabetic state develops slowly but may also not be useful if it develops rapidly. The time course is not known and needs to be investigated in a large-scale prospective study, which ideally should span over many years.

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