Effects of obesity on lipid profiles in neutered male and female cats

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Objective—To examine whether obese cats, compared with lean cats, have alterations in lipoprotein metabolism that might lead to a decrease in glucose metabolism and insulin secretion.

Animals—10 lean and 10 obese adults cats (5 neutered males and 5 neutered females each).

Procedure—Intravenous glucose tolerance tests with measurements of serum glucose, insulin, and nonesterified fatty acid (NEFA) concentrations were performed. Lipoprotein fractions were examined in serum by isopycnic density gradient ultracentrifugation.

Results—Obese cats had insulin resistance. Plasma triglyceride and cholesterol concentrations were significantly increased in obese cats, compared with lean cats. Very low density lipoprotein (VLDL) concentrations were increased in obese cats, compared with lean cats; however, the composition of various fractions remained unchanged between obese and lean cats, indicating greater synthesis and catabolism of VLDL in obese cats. Serum high density lipoprotein (HDL) cholesterol concentrations were increased in obese cats, compared with lean cats. Serum NEFA concentrations were only significantly different between obese and lean cats when separated by sex; obese male cats had higher baseline serum NEFA concentrations and greater NEFA suppression in response to insulin, compared with lean male cats.

Conclusions and Clinical Relevance—Lipid metabolism changes in obese cats, compared with lean cats. The increase in VLDL turnover in obese cats might contribute to insulin resistance of glucose metabolism, whereas the increase in serum HDL cholesterol concentration might reflect a protective effect against atherosclerosis in obese cats. (*Am J Vet Res* 2003;64:299–303)

Obesity in cats holds many pathophysiologic similarities to the same condition in humans. Obesity is frequently associated with insulin resistance, which is usually defined as an impaired ability of the hormone to suppress hepatic glucose output and to promote peripheral glucose disposal.[1,2] Obesity is a risk factor for the development of diabetes in cats.[3] It is also a risk factor for dermatologic and musculoskeletal problems.[3] We have shown that the insulin secretion pattern is abnormal in obese cats and has a pattern similar to what is seen in people with insulin resistance (ie, the acute [first] phase of secretion is lower, and the maintenance [second] phase is higher).[4-6] This is associated with impaired glucose tolerance in some obese cats.[4] Obesity in humans and other species is associated with a change in serum lipid concentrations, and lipoprotein profiles and current research in many laboratories aim to unravel the connection between altered lipid metabolism and insulin resistance. Although it has been shown that abnormalities in lipid metabolism can modulate insulin secretion from beta cells as well as the action of insulin in peripheral tissues,[2] the mechanisms are still poorly defined. Lipid abnormalities characterized by high triglyceride concentrations, high concentrations of **low density lipoproteins (LDLs)**, and low concentrations of **high density lipoproteins (HDLs)** also are a major risk factor for cardiovascular disease in people.[7,8] Few investigators have examined lipid metabolism in cats[9-13,a] by use of either density gradient ultracentrifugation or electrophoresis techniques to separate lipoprotein fractions, and to our knowledge, only a single comprehensive study[a] of lipids in obese cats has been published. The purposes of the study reported here were to characterize and compare lipid profiles in well-controlled lean and obese neutered cats and to examine whether lipid changes in obese cats could be responsible for the changes in insulin secretion and insulin resistance of glucose metabolism.

Materials and Methods

Animals—Ten male and 10 female neutered adult purpose-bred cats[b] were used in our study. Ten cats were lean and 10 cats were obese (5 neutered males and females each). Cats were maintained at the University of Georgia College of Veterinary Medicine Animal Care Facility under standard colony conditions. They were housed in individual cages and given free access to water. Animal studies were approved by the University of Georgia Animal Care and Use Committee and conducted in accordance with guidelines established by the Animal Welfare Act and the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*. Cats were determined to be healthy on the basis of results of physical examination and clinical laboratory data. All cats were familiar with daily handling. Cats were fed a commercially available dry ration[c] twice daily. Food intake was recorded at each feeding. Obese cats were allowed to eat ad libitum, whereas food intake was restricted to maintain body weight within 5% of the original weight in lean cats.

Experimental protocol—To allow blood sample collection, catheters were placed in the jugular and cephalic vein 15 to 17 hours before any tests were performed. Catheter patency was maintained by administration of 0.5 mL of 0.38% sterile citrate flush[d] every 6 hours. Blood was taken

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through the jugular catheter and allowed to clot for serum collection. After centrifugation, the serum was harvested and frozen at −20°C until assays were performed. Blood was also taken for routine CBC determination and serum biochemical analysis. **Intravenous glucose tolerance tests (IVGTTs)** were performed by use of 1 g of 50% dextrose/kg.[14]

Serum lipoprotein fractions at time 0 of the IVGTT were separated via a single isopycnic density gradient ultracentrifugation method.[15] The serum was prestained with Sudan black and ethylene glycol solution as described[10] to enhance observation of the lipoprotein fractions. A swinging bucket rotor[e] was used to centrifuge samples at 150,000 × *g* for 31 hours at 20°C. The **very low density lipoprotein (VLDL)**, LDL, subfractions of HDL (HDL_2 and HDL_3), and the very high density lipoprotein fractions were collected from the meniscus downward.

The density of each fraction was determined by weighing each fraction and measuring the volume of each fraction. In whole serum and also in each fraction, cholesterol, triglyceride, and phospholipid were measured by use of commercially available kits.[f] Protein content was determined by the method of Bradford.[16] **Nonesterified fatty acids (NEFAs)** were measured at each of the time points during the IVGTT by use of an enzymatic test kit.[g]

Measurement of weight, percent body fat, and **body mass index (BMI**; expressed in kg/m^2) was performed. The BMI was calculated as described[17] by use of the following formula:

$$\text{BMI} = \frac{\text{body weight (kg)}}{\text{body length (m)} \times \text{height (m)}}$$

where length was the distance from the point of the shoulder to the tuber ischium, and height was the distance from the point of the shoulder through the point of the elbow to the proximal boundary of the central metacarpal pad. Percent fat was measured with dual energy x-ray absorptiometry[h] For consistency in interpretation, a single investigator (JCH) analyzed scans. Scanning an external wedge composed of aluminum and thermoplastic acrylic resin calibrated against stearic acid and water ensured quality control of fat mass. Quality control scans of a phantom lumbar spinal column consisting of calcium hydroxyapatite embedded in a cube of thermoplastic acrylic resin[i] were performed before all testing sessions; the coefficient of variation was 0.29%.

Body mass index, girth, and dual energy x-ray absorptiometry measurements were taken after cats had been tranquilized.[j] All measurements were performed by the same person (JCH) to minimize variability.

Data analysis—Data were analyzed by use of software program.[k] Data are expressed as means (± SD) unless stated otherwise. The significance of differences of means between groups was evaluated by an ANOVA. A value of $P < 0.05$ was considered significant.

Results

A significant difference in body weight, BMI, and percent fat was found between lean and obese cats; however, no significant differences were found in values between males and females except for the BMI in obese cats (**Table 1**). During the IVGTT, obese cats had significantly higher serum glucose concentrations at 120 minutes than lean cats (92 ± 21 vs 71 ± 9 mg/dL, respectively; $P = 0.049$), indicating a decrease in glucose tolerance. Obese cats also had significantly higher 120-minute serum insulin concentrations than lean cats (277 ± 210 vs 111 ± 43 pmol/L, respectively; $P = 0.025$). Baseline and 120-minute serum NEFA concentrations were not significantly different between obese and lean cats (baseline values, 0.49 ± 0.15 vs 0.46 ± 0.18 mEq/L, respectively; 120-minute values, 0.24 ± 0.08 vs 0.24 ± 0.09 mEq/L, respectively). Although baseline concentrations were higher in lean females than in lean males and lower in obese females than in obese males, these differences were not significant. However, obese male cats had significantly higher baseline serum NEFA concentrations than lean males (0.54 ± 0.08 vs 0.38 ± 0.11 mEq/L, respectively; $P = 0.029$). Serum NEFA concentrations during the IVGTT were compared between female and male cats (**Fig 1**). Serum NEFA concentrations in obese male cats were

Table 1—Mean (± SD) values for body weight, body mass index and percentage fat (as measured by dual energy x-ray absorptiometry) in cats

Cats	Body weight (kg)	Body mass index (kg/m^2)	Fat (%)
Lean males (n = 5)	4.1 ± 0.7*	41.6 ± 3.5*	16.9 ± 6.4*
Lean females (5)	3.4 ± 0.5†	37.9 ± 2.9†	16.4 ± 2.1†
Obese males (5)	5.7 ± 0.7*	49.8 ± 1.9*‡	38.2 ± 5.0*
Obese females (5)	5.6 ± 0.3†	57.0 ± 3.6†‡	41.7 ± 5.4†

*Significant ($P < 0.05$) difference in values within a column between lean and obese males. †Significant ($P < 0.05$) difference in values within a column between lean and obese females. ‡Significant ($P < 0.05$) difference in values within a column between obese males and females.

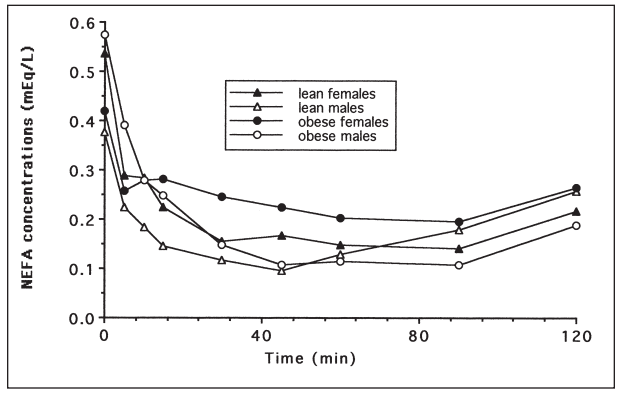

Figure 1—Mean serum nonesterified fatty acid (NEFA) concentrations verus time during the intravenous glucose tolerance test (IVGTT) in 5 lean and obese neutered female and 5 lean and obese neutered male cats.

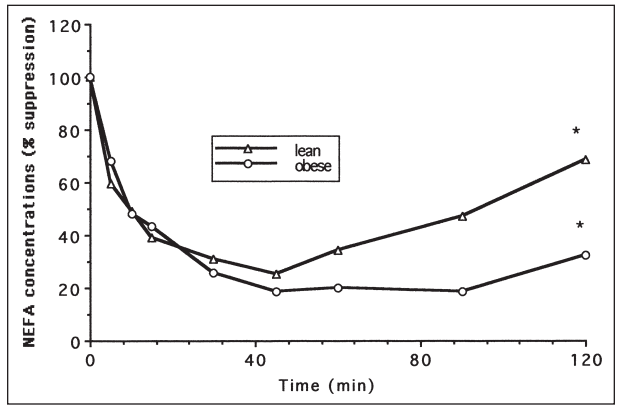

Figure 2—Percent suppression of serum NEFA concentrations during the IVGTT in 5 obese and 5 lean neutered male cats. *Significant ($P < 0.05$) difference between lean and obese cats.

Table 2—Mean (± SD) densities of serum lipoprotein fractions in neutered cats

Cats	VLDL (g/mL)	LDL (g/mL)	HDL_2 (g/mL)	HDL_3 (g/mL)	VHDL (g/mL)
Lean cats (5 males, 5 females)	0.99 ± 0.05	1.02 ± 0.03	1.08 ± 0.02	1.13 ± 0.03	1.22 ± 0.02
Obese cats (5 males, 5 females)	0.99 ± 0.05	1.01 ± 0.06	1.09 ± 0.06	1.10 ± 0.02	1.21 ± 0.05

VLDL = Very low density lipoprotein. LDL = Low density lipoprotein. HDL_2 = High density lipoprotein$_2$. HDL_3 = High density lipoprotein$_3$. VHDL = Very high density lipoprotein.

Table 3—Mean (± SD) concentration of lipids and protein in serum and serum lipoprotein fractions in neutered cats

Measurements	Serum	VLDL	LDL	HDL_2	HDL_3	VHDL
Lean cats (5 males, 5 females)	—	—	—	—	—	—
Cholesterol (mg/dL)	117.2 ± 25.2*	2.2 ± 0.7*	21.5 ± 10.3	45.0 ± 9.3*	44.3 ± 14.0*	5.7 ± 1.6
Triglyceride (mg/dL)	25.7 ± 4.6†	5.1 ± 1.5†	3.4 ± 1.2	3.9 ± 1.3	5.1 ± 1.1	9.9 ± 1.7
Phospholipid (mg/dL)	221.0 ± 40.2	1.8 ± 0.8‡	17.1 ± 7.9	80.0 ± 24.7	71.0 ± 12.3	17.0 ± 2.2
Protein (mg/dL)	7440 ± 599	0.9 ± 0.5	11.1 ± 5.7	135.7 ± 46.0	1,54.2 ± 47.6	5,223 ± 1214
Total LP mass	—	9.1 ± 3.1§	52.8 ± 21.7	254.0 ± 59.6	2,46.9 ± 28.6†	5,256 ± 1216
Obese cats (5 males, 5 females)	—	—	—	—	—	—
Cholesterol (mg/dL)	139.7 ± 22.5*	3.3 ± 1.3*	25.1 ± 12.5	59.6 ± 16.1*	62.5 ± 9.0*	5.4 ± 2.5
Triglyceride (mg/dL)	44.3 ± 11.9†	9.3 ± 3.9†	3.0 ± 2.6	4.1 ± 2.2	6.4 ± 1.3	12.1 ± 2.7
Phospholipid (mg/dL)	222.8 ± 28.8	3.3 ± 1.4‡	16.3 ± 10.5	67.4 ± 22.1	84.3 ± 16.0	16.4 ± 2.3
Protein (mg/dL)	7550 ± 685	1.5 ± 1.2	10.8 ± 7.3	108.8 ± 37.6	188.5 ± 58.0	5,496 ± 1,345
Total LP mass	—	17.4 ± 5.7§	55.2 ± 29.8	251.5 ± 81.1	310.7 ± 46.2†	5,530 ± 1,345

*,†,‡,§Significant ($P < 0.05$) difference in measurements within a column between lean and obese cats.
LP = Lipoprotein.
See Table 2 for remainder of key.

Table 4—Mean (± SD) composition of lipids and protein in serum lipoprotein fractions in neutered cats

Measurements	VLDL	LDL	HDL_2	HDL_3	VHDL
Lean cats (5 males, 5 females)	—	—	—	—	—
Cholesterol (% weight)	20.4 ± 7.7	47.2 ± 11.1	19.0 ± 8.0*	18.5 ± 5.6	0.11 ± 0.08
Triglyceride (% weight)	51.9 ± 9.0	5.8 ± 3.1	1.7 ± 0.8	1.9 ± 0.4	0.22 ± 0.03
Phospholipid (% weight)	18.7 ± 3.2	28.0 ± 4.4	27.3 ± 1.8	24.2 ± 2.1	0.23 ± 0.12
Protein (% weight)	9.0 ± 5.0	19.0 ± 7.2	48.6 ± 6.6	50.6 ± 5.8	99.4 ± 0.1
Obese cats (5 males, 5 females)	—	—	—	—	—
Cholesterol (% weight)	26.5 ± 10.3	42.1 ± 12.3	26.5 ± 7.8*	20.7 ± 3.0	0.11 ± 0.04
Triglyceride (% weight)	50.4 ± 7.0	6.3 ± 2.6	1.5 ± 0.5	1.9 ± 0.6	0.19 ± 0.03
Phospholipid (% weight)	21.1 ± 7.7	31.7 ± 7.1	27.4 ± 1.6	25.5 ± 3.9	0.34 ± 0.09
Protein (% weight)	12.0 ± 9.4	20.6 ± 4.5	44.4 ± 7.0	48.3 ± 2.6	99.5 ± 0 .1

*Significant ($P < 0.05$) difference in measurements within a column between lean and obese cats.
See Table 2 for remainder of key.

significantly more suppressed at 120 minutes during the IVGTT than in lean males ($P = 0.033$; **Fig 2**), whereas the opposite was found for female cats. However, the difference in female cats was not significant ($P = 0.059$; data not shown).

The densities of the various lipoprotein fractions were similar to that found in other studies[9,10,a] and not different between the 2 groups (**Table 2**). The concentrations of lipids and protein in serum and serum lipoprotein fractions of obese and lean cats were determined (**Table 3**), as was the composition (as mean percentage weight) of lipids and protein in serum lipoprotein fractions of obese and lean cats (**Table 4**).

Discussion

Obesity in cats is associated with substantial changes in lipid metabolism. The changes are different from obese people in some respects and similar in others. Obesity in people is often associated with dyslipidemia, which is characterized by low serum HDL and high LDL cholesterol concentrations. This constellation leads to increased cholesterol transport to peripheral tissues and is thought to be a key factor in the development of atherosclerosis.[7,8] The excessive LDL is caused by an excessive dietary intake of saturated fats and cholesterol and genetic modulation of cholesterol metabolism. It has also been shown recently that HDL cholesterol is inversely related to BMI.[8] Because HDL is involved in reverse cholesterol transport (ie, cholesterol is transported from tissues to the liver), high serum HDL cholesterol concentrations have a protective role in the development of cardiovascular disease. Cats are not prone to develop atherosclerosis, and only 2 reports[18,19] exist where atherosclerosis was induced experimentally. Our data suggest that obese cats actually may be protected from atherosclerosis, because HDL cholesterol is higher in obese cats than in lean cats. The serum HDL cholesterol concentrations are already higher in cats than in many other species in the lean state,[10] and the cat has been called an "HDL ani-

mal" because it possesses higher serum HDL cholesterol concentrations than serum LDL cholesterol concentrations.[9,13] Results of our study indicate that cats are able to increase serum HDL cholesterol concentrations even more when they become obese. It is unclear why the cholesterol concentrations in HDL_2 and HDL_3 were increased in the obese state. This may be a result of the lack of **cholesteryl ester transfer protein (CETP)**. A lack of CETP in cats has been reported[12,13] by some investigators who have been unable to measure its activity. Cats, therefore, provide an excellent model in which to study the effect of an absence of CETP on lipid metabolism. The CETP is involved in the exchange of cholesterol and triglyceride between various lipoproteins; therefore, low or absent CETP activity would result in higher cholesterol concentrations in the HDL fractions. It is also possible that an increase in the activity of lecithin-cholesterol acyltransferase or changes in phospholipid transfer protein contributed to the increased amount of cholesterol in the HDL fractions.[20] Lecithin-cholesterol acyltransferase is involved in the esterification of free cholesterol in HDL, whereas the phospholipid transfer protein mediates HDL remodeling.[21,22] Serum cholesterol concentrations were also increased in obese cats; however, it should be noted that they were still within the reference range of values in our laboratory. One might expect that long-term obesity leads to increases in cholesterol concentrations above reference range limits, but this has not been studied yet. More needs to be learned about cholesterol transport in cats to know how a high serum cholesterol concentration should be interpreted. Our data suggest that the increase in cholesterol is a positive adaptation in obese cats, because it is a result of an increase in HDL cholesterol.

In obesity and type-2 diabetes mellitus, hypertriglyceridemia is common. It is associated with insulin resistance and primarily caused by an overproduction of VLDL.[23,24] In some cases, the metabolism and clearance are abnormal, exacerbating the problem. The overproduction of VLDL may be caused by an enhanced hepatic flux of free fatty acids in the postprandial and postabsorptive states.[25] However, it also has recently been shown in a rat model that the de novo synthesis of VLDL is increased.[26,27] This was partly the result of higher endogenous fatty acid synthesis in response to increased expression of the main transcription factor of lipogenesis, a sterol-regulatory element-binding protein. In obese people, the higher VLDL synthesis and reduced LDL receptor function[28] led to increased serum concentrations of LDL that are positively correlated with an increased risk for cardiovascular disease and atherosclerosis. Obese cats had an increase in serum VLDL concentrations and its components but no change in the percent weight of each component. Also, no change in serum LDL concentrations was found. This indicates an increased VLDL particle number and an increase in VLDL catabolism. Pazak[a] has reported similar findings. Because the enzyme lipoprotein lipase is involved in the catabolism of VLDL, these results suggest that lipoprotein lipase activity might be altered in obese cats. Lipoprotein lipase is the major lipase in lipoprotein metabolism[29] and is regulated by insulin. It is most abundant in adipose tissue and muscle.[30] The enzyme is anchored in the capillary endothelium of many tissues and causes the hydrolysis of lipids primarily from chylomicrons postprandially and from VLDL. The fatty acids are then either taken up by tissues for reesterification (adipose tissue) or oxidation (muscle).[31] It is thought that modulation of tissue-specific lipoprotein lipase expression determines the partitioning of triglycerides between tissues, and it has been found in mice with overexpression of muscle-specific lipoprotein lipase that muscle triglyceride content was significantly increased.[32] It has also been shown that fatty acid oxidation is decreased in obese humans,[33] and it is now thought that the subnormal ability to oxidize fatty acids contributes to the development of insulin resistance.[6] In fact, an increase in muscle triglycerides is strongly associated with insulin resistance in people, and intramyocellular lipid concentration has been shown in a study[34] to indicate insulin sensitivity. Results of a study[35] in people revealed that intramyocellular lipid content and insulin resistance develop concomittantly. Recently, however, it has been argued that a simple causal relation does not exist, because increasing muscle triglyceride content did not lead to inhibition of insulin-stimulated glucose uptake (whole body and muscle-specific) in lipoprotein lipase-overexpressing mice.[30] It has also been determined that a redistribution of substrates to adipose tissue occurs when the insulin-receptor of muscle is deleted.[36] Glucose utilization in adipose tissue increased, which is consistent with an increase in sensitivity to insulin. These findings suggest that decreased glucose uptake in muscle predisposes to adiposity because it increases triglyceride storage by adipose tissue. The increased fat mass might secrete fatty acids, cytokines such as tumor necrosis factor-α, and leptin that could further influence glucose and fat metabolism. It is unknown whether similar changes occur in obese cats as neither tissue-specific lipoprotein lipase activity nor glucose and fatty acid uptake in insulin-responsive tissues have been studied in lean or obese cats.

Changes in serum NEFA concentrations in lean cats of our study are similar to the findings[37] described in lean cats after neutering, whereas male cats had lower baseline and higher 120-minute serum concentrations than female cats during an IVGTT. It is interesting to note that NEFA concentrations were not different between lean and obese cats when viewed as a whole, but that male cats developed significant changes with obesity. Obese male cats in our study had a significantly higher serum NEFA concentration at baseline, and the suppression at the end of the IVGTT was also significantly greater. This could indicate that obese males have greater sensitivity to the effect of insulin on fatty acid uptake. In a previous study,[37] we hypothesized that the decrease in NEFA suppression and the decreased insulin sensitivity might be contributory to the greater risk of neutered males to become diabetic. However, results of our study reported here indicate that neutered male cats respond differently than anticipated when becoming obese and have more suppression of NEFAs in response to the insulin secre-

tion elicited by the IVGTT. On the basis of results of other studies[2,38,39] in other species, the increased suppression of NEFAs could indicate a shift in insulin sensitivity that is substrate specific. It is therefore necessary to determine the fate of the NEFAs (ie, to examine whether they are oxidized or re-esterified) during steady state before a definite conclusion can be drawn. An increased re-esterification and decreased oxidation in muscle tissue might provide a link to the insulin secretory abnormalities.

[a]Pazak HE. The response of lipid metabolism and transport to a short term fast in cats: application to idiopathic feline hepatic lipidosis. PhD thesis, Department of Physoilogy and Pharmacology, The University of Georgia, Athens, Ga, 1997.
[b]Sinclair Research Center, Columbia, Mo.
[c]Purina Pro Plan, St Louis, Mo.
[d]Citric acid trisodium salt dihydrate, Sigma Chemical Co, St Louis, Mo.
[e]Beckman S 28.1, Fullerton, Calif.
[f]Sigma Chemical Co, St Louis, Mo.
[g]NEFA C, Wako Diagnostics, Richmond, Pa.
[h]QDR 100W, Infant Body software version 6, Hologic Inc, Waltham, Mass.
[i]Model DPA/QDR 1, Hologic Inc, Waltham, Mass.
[j]Telazol, Fort Dodge Animal Health, Fort Dodge, Iowa.
[k]Data Desk software for Macintosh computers, Ithaca, NY.

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