Metabolic consequences of the early onset of obesity in common marmoset monkeys

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Abstract

Objective—We assess the common marmoset as a model of early obesity. We test the hypotheses that juvenile marmosets with excess adipose tissue will display higher fasting glucose, decreased insulin sensitivity, and decreased ability to clear glucose from the blood stream.

Design and Methods—Normal and Obese (body fat > 14%) common marmoset infants (N = 39) were followed from birth until one year. Body fat was measured by quantitative magnetic resonance. Circulating glucose was measured by glucometer; insulin, adiponenctin and leptin by commercial assays. The QUICKI (a measure of insulin sensitivity) was calculated for subjects with fasting glucose and insulin measures. Oral glucose tolerance tests were conducted at 12 months on 35 subjects.

Results—At 6 months Obese subjects already had significantly lower insulin sensitivity (mean QUICKI = .378±.029 versus .525±.019, N=11, p=.003). By 12 months Obese subjects also had higher fasting glucose (129.3±9.1 mg/dL versus 106.1±6.5 mg/dL, p=.042) and circulating

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Previous findings:

Adult obese marmosets have deficits in glucose metabolism.

Marmosets can display obesity as early as 6 months of age.

Birth weight influences the extent of obesity at 12 months, suggesting in utero effects.

Findings from this study:

Obese young marmosets display deficits in glucose metabolism by 6 month, which worsen by 12 months.

In obese young marmosets birth weight affects leptin metabolism at 12 months, suggesting in utero effects on metabolism.

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adiponectin tended to be lower (p=.057). Leptin was associated with percent body fat; however, birth weight also influenced circulating leptin. The OGTT results demonstrated that Obese animals had a decreased ability to clear glucose.

Conclusions—Early onset obesity in marmosets results in impaired glucose homeostasis by one year.

Keywords

insulin sensitivity; glucose; leptin; adiponectin

Introduction

Childhood overweight and obesity is a growing concern in the world with an average rate of 11.7% (95% CI: 8.9 – 15.3%) in developed countries and 6.1% (95% CI: 5.0 – 7.2%) in developing nations resulting in approximately estimated 43 million overweight or obese children under the age of 5 years in the world.[1] The proportion of preschool-aged (2-4 years old) children in the U.S. classified as obese is approximately 15%.[2] Among 4 year olds the estimated prevalence of obesity in the U.S. is over 18%, ranging from 12.8% in Asian Americans to 31.2% in American Indians.[3] Childhood obesity is associated with an increased risk of adult obesity and of early life occurrence of diseases that have been associated historically with middle- and late- age in humans, such as Type 2 diabetes.[4]

Animal models to study the causes and consequences of obesity during infancy in humans would be valuable. Rodents, as efficient and tractable models have provided the primary testing ground for studies of obesity.[5,6] However, rodent models have limitations when applying findings to humans including phylogenetic differences in fat cell function and distribution; development and circadian rhythm of feeding behavior; and functions of some adipokines (e.g. resistin) between rodents and humans.[7-10] In terms of the study of pediatric obesity, the strikingly different patterns between mice and primates of pre- versus post-natal growth and of post-natal growth dependence upon milk versus post-weaning nutrition places some limits on the usefulness of rodent models.[11] Therefore, nonhuman primate models of pediatric obesity may be of value to examine primate-specific aspects of pre- versus post-natal growth on obesity development and to validate findings from rodents in a model system more closely resembling humans, but offering control over genetic and environmental factors that is generally lacking in human studies.

There are substantial practical problems associated with tracking growth parameters in neonatal and pre-weaning nonhuman primates, even in a captive setting and, for this reason very little is known regarding development of early life adiposity in mother-reared monkeys and apes. However, because of its small size, relative ease of handling (and fast life history), the common marmoset, a New World monkey, offers important opportunities in this area of research.[11] Marmoset infants begin weaning at around 30 days of age and are completely weaned by around 70-80 days of age. They begin puberty between 11 and 14 months of age and are fully reproductively competent by around 18 months of age. Stable adult weights are generally attained by two years of age.[12] In the wild, adult marmosets average 320 to 336 grams.[13] The average weight of adult captive animals ranges from 283 to 530 grams, with

most animals historically being in the range of 350-400 grams.[14] However, we have observed a consistent increase in the number of high-weight, high-fat animals in our colony over a 14 year period. Mean early adult weight in our colony is now close to 400g, and the proportion of adult animals with body weights above 450g has greatly increased.

Recent publications, by our group and others, have described phenotypes associated with obesity in adult marmosets, including metabolic dysfunction and dyslipidemia.[14,15] For example, adult marmosets with body fat percentages above the 80th percentile had significantly elevated glycated hemoglobin (HbA$_{1c}$ and fasting glucose, triglycerides and very low-density lipoproteins (VLDL). We have previously developed successful protocols for removing, handling and returning infants to their family group and published results of a study examining the development of obesity at an early age in the common marmoset documenting the onset of obesity before one year of age in about half (51.6%) of the infants followed in the study.[16] Here we present data on metabolic parameters (glucose, insulin, leptin and adiponectin) for marmosets at 6 months and one year of age and compare the values from marmosets with normal percent body fat to values from marmosets with excess adipose tissue, based on our previous findings.[16] We test the hypotheses that animals with excess adipose tissue will display higher circulating leptin, lower circulating adiponectin, higher fasting glucose, decreased insulin sensitivity, and decreased ability to clear glucose from the blood stream.

Methods and Procedures

The study was conducted between January 2008 and July 2011 at the Southwest National Primate Research Center (SNPRC) in San Antonio TX, and was approved by the Animal Care and Use Committee of SNPRC. Basic details on housing and husbandry have been previously described.[17] All dams in this study were between 3 and 6 years of age and had produced at least one successful litter prior to the birth of the infants in this study. Most of the dams were of normal weight and body fat (75%) and 25% were considered obese based on our previous work.[16] All infants were housed with their parents plus older offspring. Animals were fed either the standard diet mix fed to the entire colony (Normal mix; approximately 12% of metabolizable energy from fat and 71% from carbohydrate) or a modification of that mix that included Normal mix plus the standard diets formulated with increased fat content (High-fat mix; approximately 38% of metabolizable energy from fat and 45% from carbohydrate). Protein (17% of metabolizable energy) and other nutrients were kept constant on a per-energy basis between the two diet mixes. Marmosets begin to consume solid food at around 30 days of age; are completely weaned at somewhere between 70 and 80 days of age; and begin puberty at 11-14 months of age. Based upon a comparison of this weaning and maturation pattern to humans, a 30 day old marmoset may be considered equivalent to a 5-8 month old human infant, a 180 day (6 month) old marmoset may be considered equivalent to a prepubertal child – i.e. a juvenile, and a 12 month old marmoset similar to a human adolescent.

Body composition (lean and fat mass) was assessed at approximately 6 and 12 months of age via quantitative magnetic resonance imaging (QMR) using an Echo Medical System (Houston, TX) MRI unit accommodating animals from approximately 100 to 800 grams.

This system has been extensively validated for mice[18] and the detection methodology used in the marmoset system is identical to that used in the mouse system, with only the volume of the homogenous magnetic region differing. Unsedated animals were placed in a plastic tube, which was then inserted into the magnetic chamber. Scans took < 2 min, on average, for each animal. Repeat scans on 12 marmosets (adults and juveniles, lean and obese animals) found the repeated fat and lean mass values were highly correlated (r=.999 and r=.998 for fat and lean mass, respectively) and that fat mass values differed by only 0.2±0.4% between scans.

Although adiposity is a continuous parameter, research in humans typically presents results in terms of categories, ranging from many categories (e.g. Underweight, Normal weight, Overweight, Obese, Very obese), to only two categories (Obese versus not Obese). Given our objective to assess marmosets as models for human early obesity we have chosen to categorize our subjects; given our sample size we chose the conservative option of only two categories. Based on our previously published results, to wit, among juvenile marmosets with 14% body fat or greater, fat mass increased by 0.468g of fat per gram lean mass compared to 0.318g of fat per gram lean mass for juveniles with less than 14% body fat and 0.338g fat per gram lean mass for normal weight adult females,[16] we classified marmosets in this study at 6 months and 12 months of age as Normal (body fat < 14%) or Obese (body fat < 14%).

Fasting glucose

Following an overnight fast, subjects were manually captured and transferred into a tube-restraint device used for blood collection. The animals had been habituated to this procedure prior to sampling. A 2ml blood sample was collected from the femoral vein using a heparin coated needle and syringe. A drop of this blood was used to assess glucose via a FreeStyle glucometer. The rest of the blood sample was emptied into a plain centrifuge tube. Samples were immediately centrifuged at 8,000 rpm for 8 minutes. Plasma was pipetted into aliquots for storage at -80C until assayed for endocrine concentrations.

OGTT

Following an overnight fast subjects were manually captured and transferred into a tube-restraint device used for blood collection to which they had previously been habituated. Butterfly needles (23 gauge) with shortened catheter tubes were used to perform tail vein sticks throughout the procedure. Blood was drawn by tail stick at times 0 (just before administration of the oral glucose challenge), 15 minutes, 30 minutes, 60 minutes and 120 minutes post dose. A drop of blood was used to determine glucose concentration via glucometer. Animals received an oral glucose dose that consisted of a 40% dextrose and water solution. Each animal received a calculated glucose dose equal to 0.5% of their current body weight. Subjects remained in the restraint tube for the 15 and 30 minute blood draws. Subjects were removed from the tube following the 30 minute draw and placed in a transport box. Prior to the 60 minute draw they were removed from the box and placed back in the restraint tube. This was repeated for the 120 minute draw. Subjects were returned to their family group following the 120 minute blood collection.

Endocrine assays

Assays for leptin, adiponectin, and insulin were performed at the Wisconsin National Primate Research Center Assay Service Laboratory. Due to plasma sample volume not all subjects could be measured for all hormones. Insulin levels were determined by a porcine insulin RIA (Millipore, Billerica, MA) that has been validated for the marmoset previously (Ziegler et al., in press). Samples were run at a volume of 50 μl in duplicate. Coefficient of variation, CV, for inter and intra, respectively, were 4.89 and 2.87. Leptin levels were determined using the Human Leptin RIA (#HL-81K, Millipore, Billerica, MA). Samples were run in duplicate at 100 μl volumes. The CVs were 9.9 and 6.71 for inter and intra-assays. Both the total adiponectin and the high molecular weight values were measured for marmosets using the Adiponectin ELISA (#47_ADPHU-E01, ALPCO Diagnostics, Salem, N using a 10 μl serum sample. Details of these analyses are provided in Ziegler, et al (in press).[19] The CVs for total adiponectin were 6.1 and 1.5 (inter and intra-assay) and for high molecular weight adiponectin were 6.1 and 1.5, respectively.

QUICKI

The quantitative insulin sensitivity check index (QUICKI) is a measure of insulin sensitivity in humans that has been validated against the hyperinsulinemic euglycemic glucose clamp technique and is calculated as: $1/[\log(\text{fasting insulin}) + \log(\text{fasting glucose})]$.[20] It has been validated and used successfully in other nonhuman primate species such as the rhesus macaque, where it was found to better predict clamp results compared to the homeostasis model assessment (HOMA) index.[21] We calculated QUICKI for all subjects with both a fasting glucose and fasting insulin value at 6 months and at one year of age.

Statistical analyses

All values are presented as the mean±SEM. The relationships among metabolic parameters and physical parameters were investigated using correlation and regression. Differences in parameter values between Normal and Obese subjects were tested using ANOVA and ANCOVA. Results were considered statistically significant if p<.05.

Results

About half (46.2%) of the subjects in this study were categorized as Obese at one year of age (18 of 39); all Obese subjects had greater than 15.5% body fat. Among Normal subjects, the two animals with the highest body fat (12.6% and 13.2%) appeared to be intermediate between the Obese and the other Normal subjects in terms of fat-to-lean body mass (Figure 1). All other Normal subjects were at or below 11% body fat.

Blood samples matched with body composition measurements were collected from 33 subjects at 6 months of age, resulting in values for blood glucose for 32 subjects, leptin for 31 subjects, insulin for 11 subjects and adiponectin for only 3 subjects. At one year of age blood samples matched with body composition measurements were collected from 39 subjects, resulting in values for blood glucose for all 39 subjects, leptin for 37 subjects, insulin for 23 subjects and adiponectin for 29 subjects. QUICKI was calculated for all subjects with both a fasting glucose and fasting insulin value (N = 23).

6 months of age

Although at 6 months there was no significant correlation between percent body fat and fasting glucose (r=.215, p=.236), animals with more than 14% body fat had higher fasting glucose (140.8±19.2 mg/dL versus 101.1±7.4 mg/dL, p=.036). However, after excluding the one very high and probably anomalous value in an Obese subject (350 mg/dL), this result was only a tendency (123.3±8.7 versus 101.1±7.4, p=.063). Insulin was positively correlated with percent body fat (r=.696, p=.017) and the QUICKI index calculated for the 11 subjects with insulin data showed a significant negative correlation with percent body fat (r=-.842, p=.001; Figure 2). Obese subjects had significantly lower insulin sensitivity compared to Normal subjects (mean QUICKI = .378±.029 versus .525±.019, p=.003). Leptin showed no association with percent body fat (r=.140, p=.453), and did not differ between the groups at this age.

One year of age

At 12 months of age fasting blood glucose was correlated with percent body fat (r=.395, p=.013), and Obese subjects had higher fasting glucose than did Normal subjects (Table 1). Glucose values were not correlated with insulin, leptin, or adiponectin. Fasting blood glucose values for Normal and Obese animals did not differ for the two different measurement times in this study (at the one year QMR fat measurement and time 0 for the OGTT at one year of age, P>.4 for all comparisons). However, the fasting glucose values for these two time points were not significantly correlated (r=.252, p=.143) and values for Obese animals were not different from those of Normal subjects at the OGTT time 0 (see below for OGTT values).

Insulin was positively correlated with percent body fat (r=.664, p=.001; Figure 3) and QUICKI was negatively correlated (r=-.879, p<.001; Figure 4). Obese subjects had significantly higher insulin and lower QUICKI (Table 1). For the two Normal subjects with the highest body fat, the QUICKI value for the animal with 13.2% fat fell within the range of the other Normal subjects while the value for the subject with 12.6% fat was similar to that of the Obese subjects (Figure 4). In Normal subjects insulin did not change between 6 and 12 months of age and was not correlated with body fat. In Obese subjects insulin increased with age (r=0.529, p=.011), which is mostly explainable by the increase in insulin at 1 year for subjects with percent body fat over 14%.

Total adiponectin tended to be negatively correlated with percent body fat (r=:.362, p=.054) and to be lower in subjects with >14% body fat at one year of age (p=.057). When the two Normal subjects with the highest body fat (Figure 1) were excluded, the difference was significant (10.2±1.6 μg/ml versus 6.5±.7 μg/ml, p=.041). However, when only the high molecular weight adiponectin was considered there was no difference (Table 1).

Leptin was correlated with percent body fat at one year of age (r=.493, p=.002), however there were 4 Normal and 4 Obese subjects with anomalously low leptin scores (Figure 5). Obese subjects had higher leptin values than did Normal subjects, on average (Table 1). When adding percent body fat into the model, the ANCOVA results indicate that Obese and Normal subjects have the same relationship between leptin and percent body fat, and the

relationship is significant (p=.027). In Normal subjects percent body fat decreased with age (mean of -2.4%; p=.001); indeed, on average Normal subjects had the same fat mass at 6 and 12 months of age (22.8±3.1g versus 19.2±2.3 g; p=.180). In Obese subjects fat mass increased by 37.1±5.5g between 6 and 12 months (p<.001) and percent body fat increased by 4.2±1.3% (p=.006). These differences between groups were significant (p<.001). However, in both groups leptin appeared to increase with age (Normal subjects mean increase = .08±.16 ng/ml; Obese subjects mean increase = .28±.18 ng/ml), although the differences were not significant (p>.1). Interestingly, birth weight was correlated with leptin at one year of age (r=.350, p=.034), even though birth weight was not correlated with percent body fat (r=.033, p=.842). A linear regression using percent body fat and birth weight to predict leptin at one year found both factors to be significant (p=.002 and p=.031, respectively; R^2=.341). Although maternal obesity and maternal access to the High-fat mix were independently associated with high birth weight, neither of these factors was significantly associated with any of the measured endocrine factors either separately or after controlling for percent body fat.

There were nine subjects (3 Normal and 6 Obese at 12 months) with QUICKI values at both 6 and 12 months of age and two subjects with values at 12 months and 18 months (1 Normal at both time points, the other Obese at 12 months but Normal at 18 months after weight loss). There was a significant negative relationship between the change in percent body fat and the change in QUICKI between the two time points (Figure 6).

The results of the oral glucose tolerance tests indicate that Obese subjects (14% body fat or greater) had poorer glucose control than did Normal subjects (Figure 7). Pre dose fasting glucose values did not differ between Obese (N = 16) and Normal (N = 19) subjects (120±11 mg/dL versus 110±8 mg/dL, p=.464), but Obese subjects had a faster rise in blood glucose, with significantly higher mean values at 15 minutes (159±13 mg/dL versus 121±11 mg/dL, p=.032) and 30 minutes (173±15 mg/dL versus 136±10 mg/dL, p=.043) post dose. Blood glucose for both Obese and Normal subjects peaked at 60 minutes at about 1.7 times fasting levels with no significant difference between the groups. By 120 minutes Normal animals had returned to baseline glucose values (110±14 mg/dL), but Obese animals had significantly higher glucose values (154±23 mg/dL, p=.016), about 1.3 times baseline on average.

Discussion

Defining obesity is a complex endeavor. With a sample size of 39 we caution that it is difficult to make fine distinctions between young marmosets that are on the high-fat side of normal and the low-fat side of obese. We have previously described evidence of metabolic dysfunction in adult marmosets that were above the 80th percentile in the proportion of body fat.[14] Even though marmosets are a monomorphic species (there was no sex difference in this study), in our previous study there were more females with high percent body fat than males. Using the 80% criteria within each sex, obesity in adult males corresponded to 14% body fat or greater while for adult females the value was 17% body fat. Our definition of obesity for young marmosets is based upon a different relationship between fat and lean mass for animals above 14% body fat.[16] However, we note that all but two of the subjects

classified Obese in this study had body fat above 17%, with the lowest value being 15.5%. Thus, most of these subjects would have been classified as obese by all of our definitions. Still, we are dividing our animals into only two groups, and further research that increases sample size may well distinguish subtler categories between Normal and Obese.

We have also documented that obesity in young marmosets occurs as early as 6 months of age, and that on average animals that are above 14% body fat at one year of age already had higher body fat as early as one month of age.[16] These data demonstrate that marmosets classified as obese as juveniles (12 months of age with 14% body fat or greater) exhibited signs of impaired insulin sensitivity, including possibly higher fasting blood glucose (true for one of two time points tested), elevated fasting insulin levels, and a tendency to have lower circulating adiponectin. Even though the difference in fasting glucose is small, the difference in fasting insulin results in significantly different measures of insulin sensitivity at 6 and 12 months of age (Figures 2 and 4). Thus, Obese young marmosets are secreting more insulin in order to maintain fasting glucose levels close to that of Normal young marmosets. When subjected to an oral glucose tolerance test (OGTT) Obese subjects had a more rapid rise in blood glucose and elevated blood glucose at 120 minutes, a time point when Normal animals had returned to baseline blood glucose levels. These results taken together indicate that the early onset of obesity has significant negative metabolic consequences for one-year old marmosets, with animals above 14% in body fat displaying evidence of a reduction in insulin sensitivity and greater difficulty maintaining glucose homeostasis. The more limited data from 6 month old marmosets suggests that this pattern is already beginning to be established at that early age.

The results of the OGTT trials come with a minor caveat. Because the glucose dose was set by body weight (0.5% of body weight), Obese animals received a higher dose of glucose if expressed on a lean body mass (LBM) basis (0.59 – 0.67% versus 0.52 – 0.57% for Normal subjects). It is not certain whether adjusting the glucose challenge dose by body weight or by lean body mass is more appropriate, however, rodent studies have typically used body weight.[22] The higher glucose dose per LBM might partly explain the faster rise in blood glucose at the beginning of the OGTT in Obese subjects, however, there was no correlation between the dose per lean mass and blood glucose values for either Normal or Obese subjects at 15 or 30 minutes (data not shown).

The mean fasting insulin concentration for juvenile marmosets with normal percent body fat ($1.01\pm.25$ μU/ml) is similar to that we previously reported for lean/normal adults (1.47 μU/ml). The fasting insulin concentrations for older, obese marmosets (33.8 μU/ml) averaged roughly twice the value of obese juveniles (16.45 μU/ml).[23] These results, though cross sectional, support the contention that insulin resistance associated with high adiposity begins in young marmosets and continues to worsen throughout the lifespan in a fashion similar to that observed in humans. The timeline across which this insulin resistance may develop into diabetes in this species is yet to be determined. However we have documented uncontrolled hyperglycemia over a three year period in an adult marmoset obese at 5 years of age, associated with hepatic steatosis, increased hepatic glycogen storage, fibrotic changes in the kidney and cerebral microvascular hemorrhages resulting in death before 8 years of age. In addition, one of the obese juveniles of this study died at 17 months of age (roughly

equivalent to 20 years in humans) from cardiomyopathy due to cardiomegaly. Other researchers also have found a high prevalence of obesity in subadult (1-2 year old) captive marmosets and that dietary manipulations, particularly of simple carbohydrates, can enhance fat gain and lead to impaired glucose tolerance and pancreatic islet hyperplasia.[15] They also found that high fat diet feeding, while not enhancing fat gain, did result in atherosclerotic changes.

Leptin was correlated with body fat, though several animals, both Normal and Fat, had anomalously low values suggesting that they may have physiologically responded to fasting by down regulating leptin synthesis, similar to results in fasting rats and humans.[24,25] The result that birth weight had a significant effect independent of body fat on circulating leptin at 12 months of age suggests the hypothesis that in utero factors may influence the relationship between body fat and leptin secretion later in life. Leptin dysfunction has previously been described for mice that are exposed to chronic postnatal overfeeding. Leptin resistance was noted in the arcuate nucleus as early as day 16 of life, even in the presence of normalized circulating leptin concentrations.[26] The analogous stage of development for marmosets would occur in utero, suggesting the hypothesis that changes in leptin metabolism due to high nutrient flow across the placenta might affect feeding behavior in marmosets later in life. We have documented subtle differences in feeding behaviors between these Obese and Normal marmosets in the first year of life.[27]

The proportion of young marmosets that were classified obese by one year of age was quite high (46.2%). In part this was likely due to our only having two categories: Normal and Obese. However, in this study we deliberately selected obese dams to comprise half of our maternal sample, and we offered the High-fat diet mix from before pregnancy through the first year of life to half the subjects. Both maternal obesity and access to the High-fat mix were significantly associated with higher birth weight and the likelihood of becoming obese by one year.[16] We may have produced an excess of obese subjects compared to what would have occurred under normal husbandry practices. However, researchers at the New England Primate Research Center recently documented obesity in 46% of 1-2 year old marmosets in their colony.[15] Obesity may be epidemic among captive marmosets.

These findings, taken together, support the contention that further characterization of obesity development and associated metabolic dysfunction in this small, rapidly maturing nonhuman primate species may lead to a valuable model in which to test therapeutics and interventions for pediatric or juvenile obesity and metabolic dysfunction.

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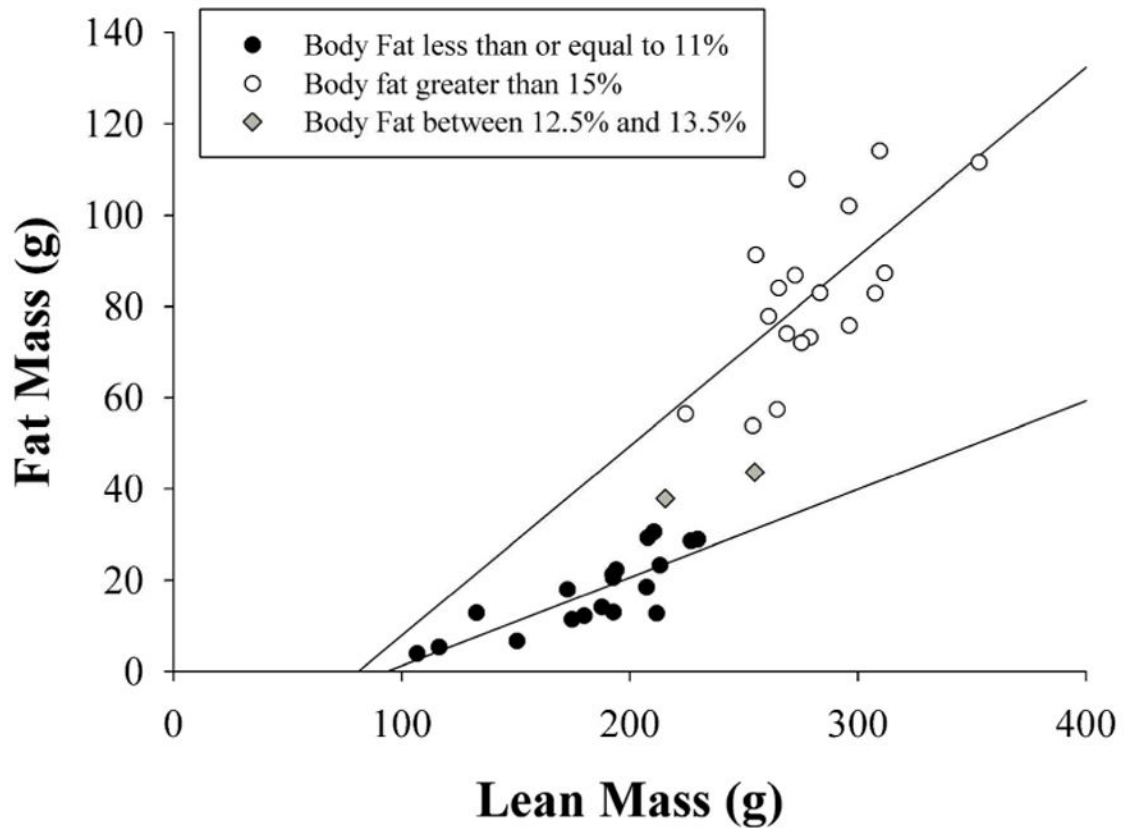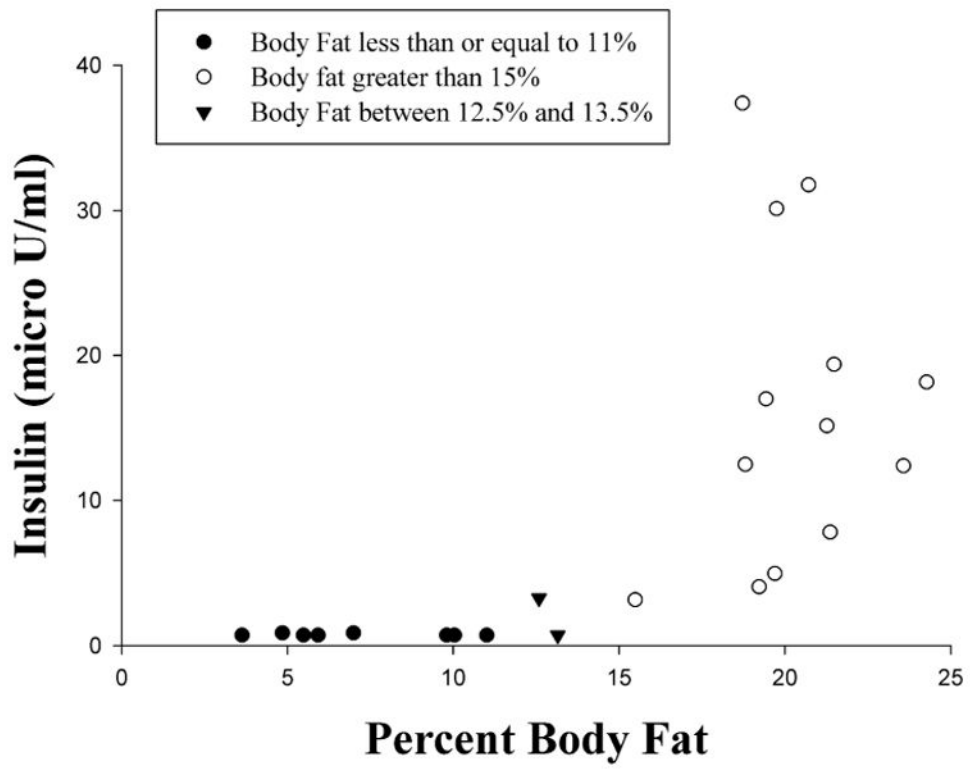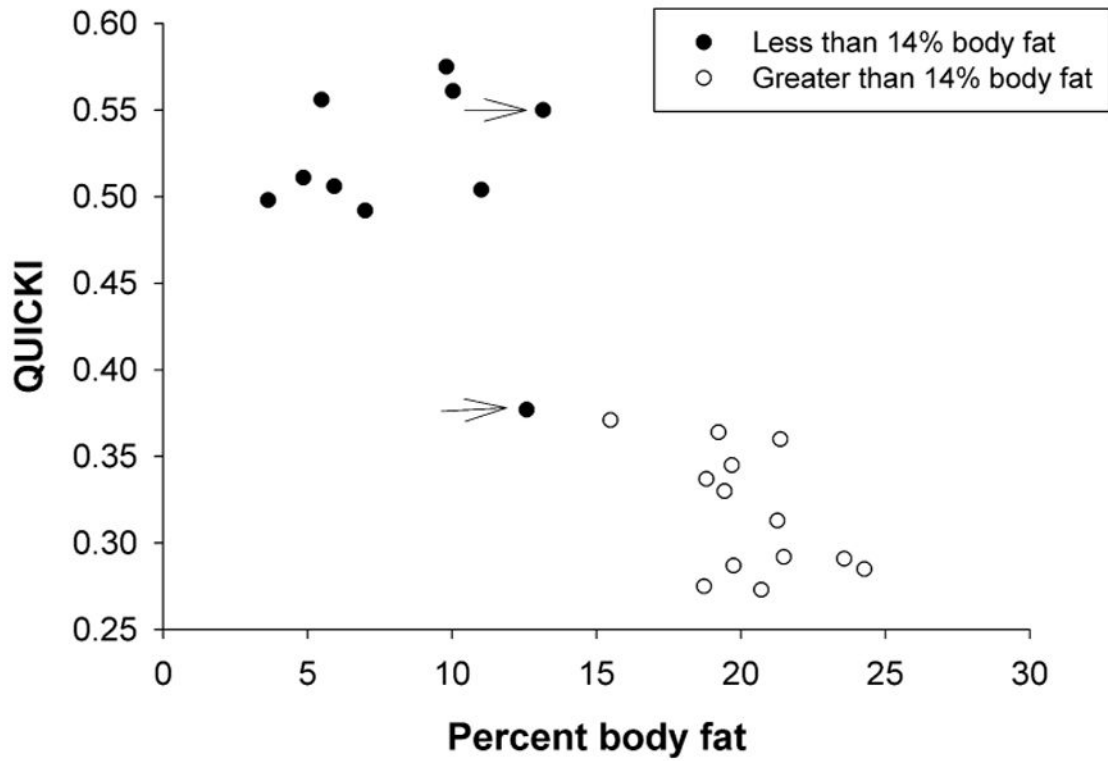
Figure 1.
The relationships between fat mass and lean mass for Obese subjects (open circles; N=18; all with body fat above 15%) and Normal subjects (Filled circles; N=19; all with body fat less than or equal to 11%). The two subjects with body fat between 12.5% and 13.5% (filled triangles) are classified as Normal, but were not included in either regression line.
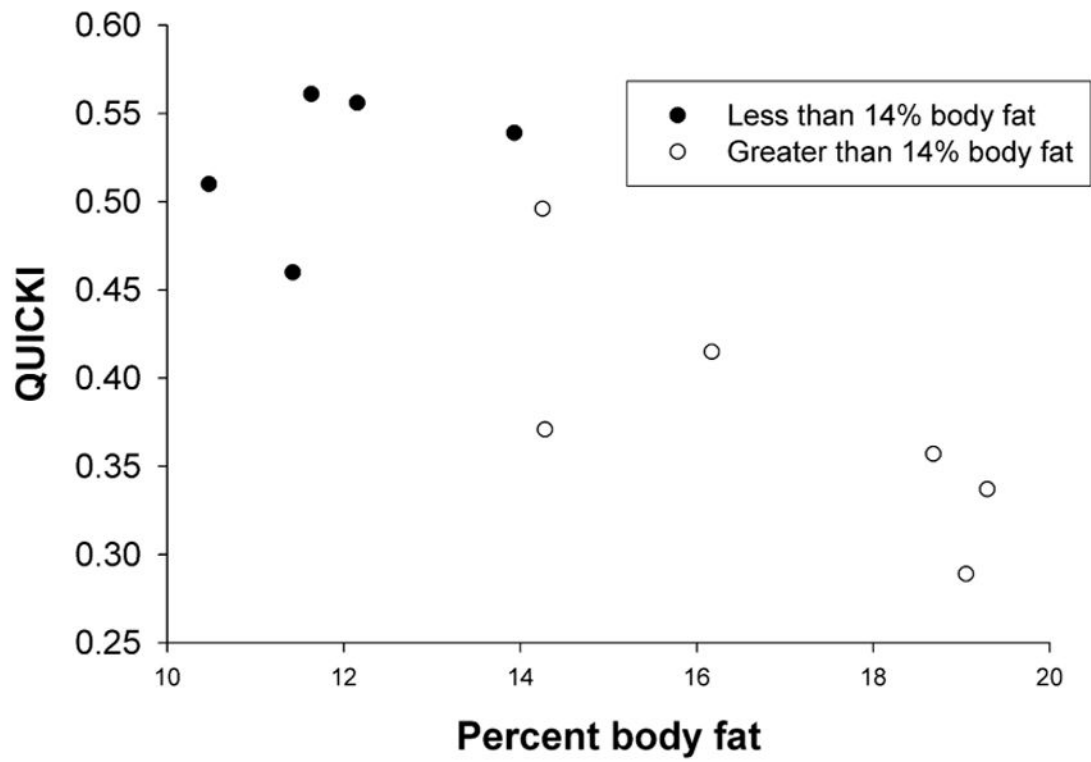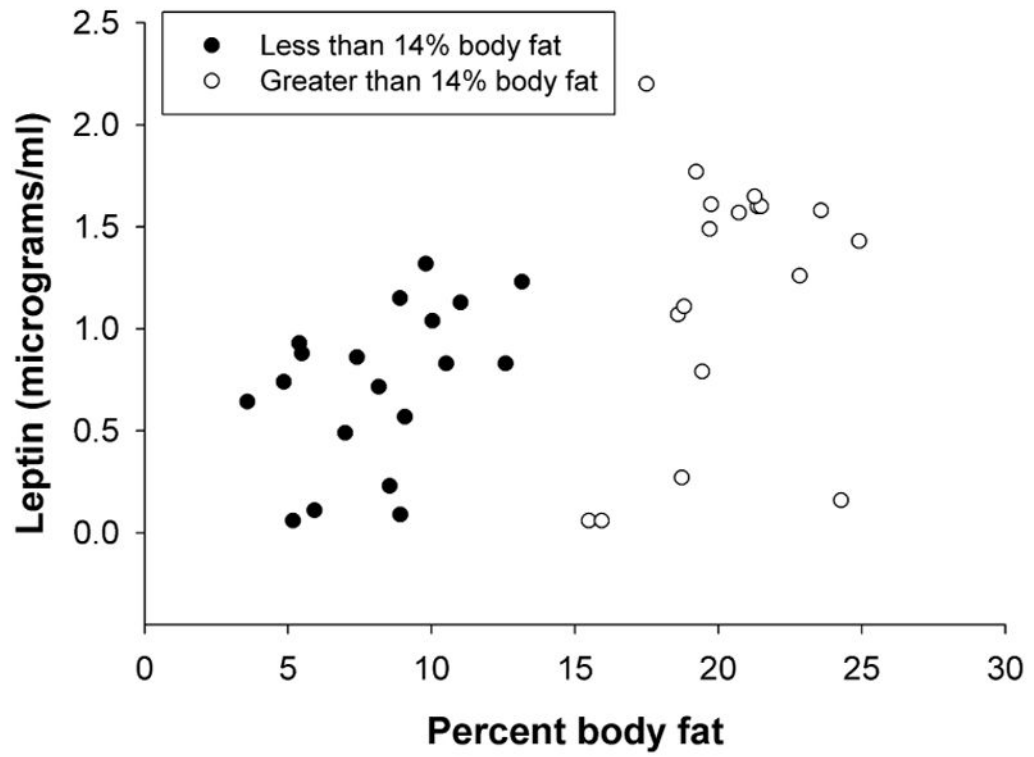
Figure 2.
QUICKI by percent body fat at 6 months of age. Filled circles are Normal subjects and open circles are Obese subjects.

Figure 3.
Insulin by percent body fat at one year of age. Filled circles and triangles are Normal subjects as in Figure 1 (N = 10) and open circles are Obese subjects (N = 13).
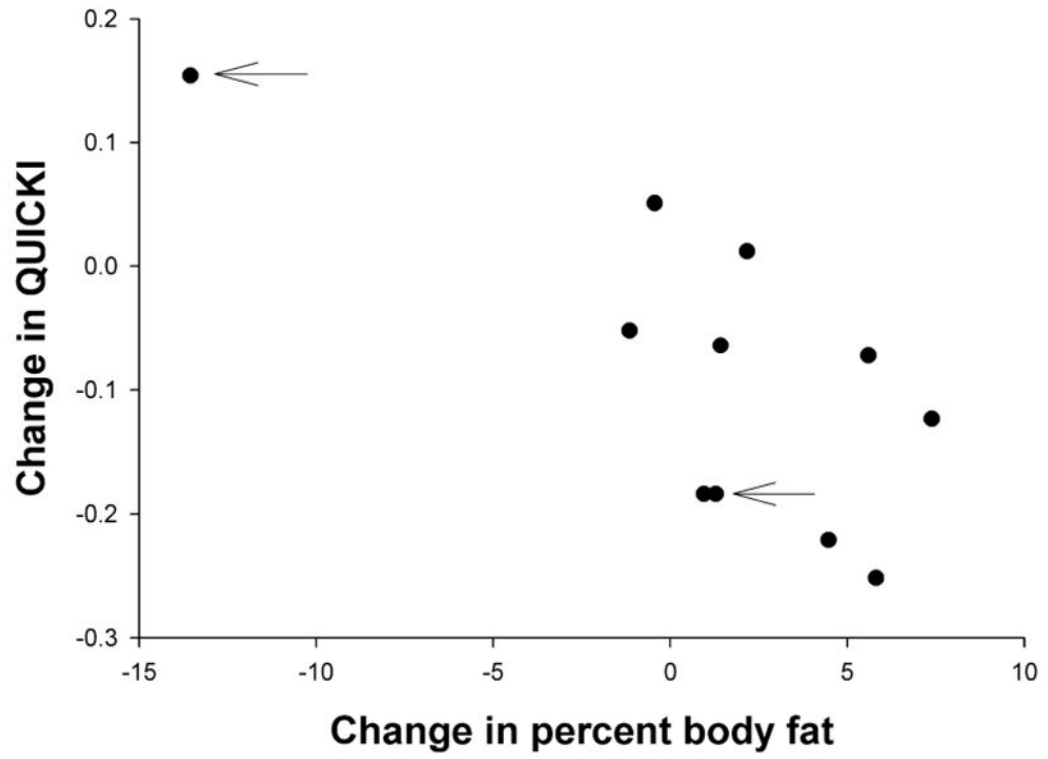
Figure 4.
QUICKI by percent body fat at one year of age. Filled circles are Normal subjects (N = 10) and open circles are Obese subjects (N = 13). The two arrows indicate the Normal subjects with the highest body fat (12.6% and 13.2%).
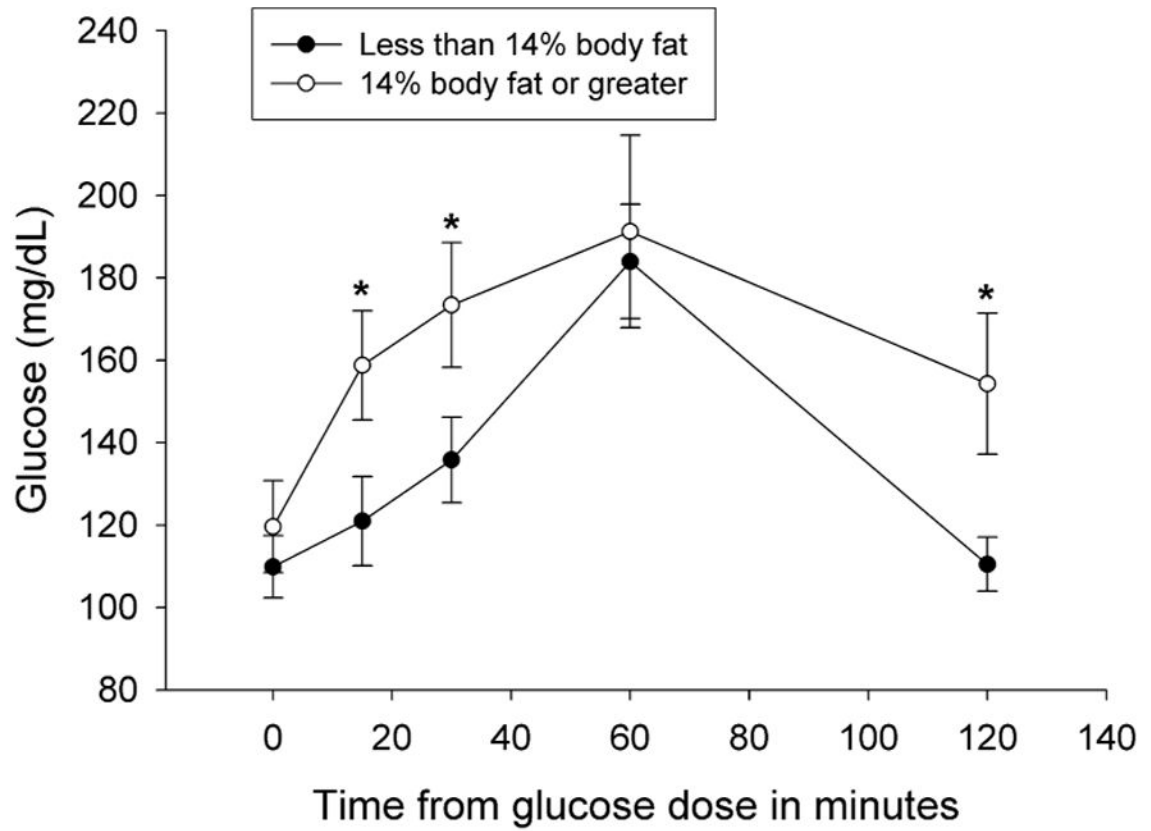
Figure 5.
Leptin by percent body fat at one year of age. Filled circles are Normal subjects (N = 19) and open circles are Obese subjects (N = 18).

Figure 6.
The change in QUICKI versus the change in percent body fat over 6 months with older subjects indicated by arrows.

Figure 7.
Results of oral glucose tolerance tests of Normal (filled circles; N = 19) and Obese (open circles; N = 16) subjects at one year of age. Statistically different values are marked by *.

Table 1

Values for metabolic parameters in Normal and Obese marmosets at 12 months of age.

	Normal animals	Obese animals	P value
Glucose	106.1±6.5 mg/dL	129.3±9.1 mg/dL	.042
	N = 21	N = 18	
Insulin	1.01±.25 µU/ml	16.45±3.04 µU/ml	<.001
	N = 10	N = 13	
QUICKI	.513±.018	.317±.010	<.001
	N = 10	N = 13	
Leptin	.73±.09 ng/ml	1.18±.15 ng/ml	.014
	N = 19	N = 18	
Adiponectin	9.83±1.54 µg/ml	6.53±.71 µg/ml	.057
	N = 14	N = 15	
High molecular	1.10±.24 µg/ml	.80±.13 µg/ml	.294
weight Adiponectin	N = 14	N = 14	