EFFECT OF HIGH-FAT DIET ON BODY COMPOSITION AND HORMONE RESPONSES TO GLUCOSE TOLERANCE TESTS IN GROWING RATS

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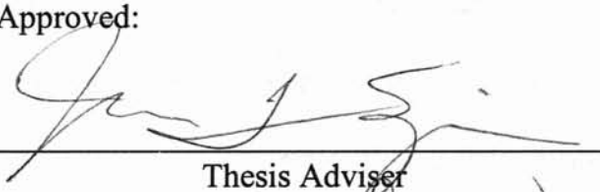

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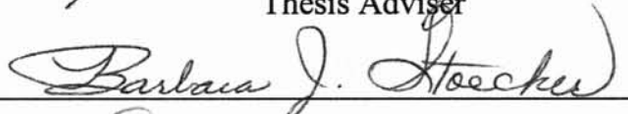

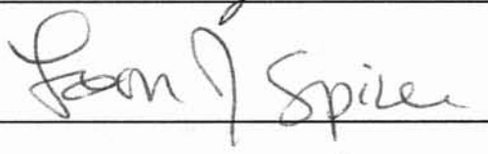

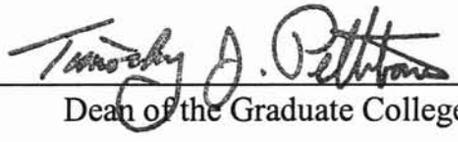

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LIST OF ABBREVIATIONS

AUC	Area under the curve
BG	Blood glucose, whole blood glucose
BMI	Body mass index
BW_{kg}	Body weight in kilograms
CV	Coefficient of variation
DM	Diabetes mellitus
DXA	Dual X-Ray Absorptiometry/ Dual X-ray Absorptiometry Analysis
GH	Growth hormone
h	hour/ hours
HF	High-fat diet/ fed
IR	Insulin resistant
IS	Insulin sensitive
IVGTT	Intravenous glucose tolerance test
LF	Low-fat diet/ fed
min	minutes
OGTT	Oral glucose tolerance test/ Oral glucose challenge
OHA	Oral hypoglycemic agents
SAS	Statistical Analysis System
SD	Sprague-Dawley

CHAPTER I

INTRODUCTION

"In developing countries, as their economies grow, non-communicable diseases will become more prevalent largely because of the adoption of 'western' lifestyles and their accompanying factors—smoking, high-fat diets, lack of exercise."

(The World Health Report 1998) (1)

Overweight and obesity are associated with a variety of health maladies, including cardiovascular diseases such as hypertension, stroke, coronary artery disease, type 2 diabetes, and cancers—all factors affecting quality of life for those affected by them. Obesity, especially central or android obesity, has been identified as the foremost contributing factor to insulin resistance (2;3).

Insulin resistance is the impaired ability of insulin to stimulate glucose uptake by cells and to suppress glucose production by the liver. Hyperinsulinemia, an abnormally high level of insulin in the blood, is one characteristic of impaired insulin sensitivity, and may be accompanied by elevated levels of glucose in circulation. The net effect is less glucose clearance for a given amount of insulin in the blood. There is also an increase in the utilization of fatty acids, especially by muscle. Type 2 diabetes, which often develops within ten years of the onset of insulin resistance, is a result of untreated insulin resistance, followed by a decrease in insulin production by the pancreatic ß-cells (4-6).

In industrialized nations such as the United States, highly refined, high-fat diets are common. In the US, total caloric intake has increased since the 1970's, due in part to higher consumption of added fats such as salad dressings and cooking oils (7). At 33% of

calories, this is still above fat intake recommendations outlined in the Dietary Guidelines for Americans (8), which are associated with lower rates of lifestyle-related chronic illnesses (9). With this increase in fat and calorie intake over time, there has been an increase in the incidence and prevalence of overweight and type 2 diabetes mellitus in persons who are overweight and obese (10). This same increase in incidence is seen in Asian peoples at body mass indexes considered acceptable for northern Europeans and Americans (4).

Subjects with type 2 diabetes who were able to lose excess weight had increased insulin sensitivity, decreased hepatic glucose output, and increased insulin sensitivity, confirming a relationship between adiposity and insulin resistance (3;11;12).

Diets high in fat are known to increase body weight and fat mass, induce alterations in carbohydrate and lipid metabolism, lead to insulin resistance, and increase production and release of the hormone leptin in humans, rodents, and other animals (13-17).

Leptin, which is produced and released by adipocytes, exhibits a diurnal pattern of presence in the blood (18-20), is significantly correlated to insulin resistance (21;22), and is released in response to increased insulin levels in the blood (23;24). Leptin inhibits insulin secretion (25-28), provides an increased sensation of satiety in normal weight individuals (20), and decreases food intake in laboratory animals (29-32). Since it is produced by adipose tissue, systemic leptin concentrations are positively correlated with fat mass(3;33;34). Obese individuals produce twice the amount of leptin compared to slender individuals, and there is evidence indicating this is due to increased production of leptin by subcutaneous adipocytes compared to visceral fat cells (35;36). There is clear

indication that gender hormones are related to leptin levels in the blood as early as infancy (37) and in relation to sexual maturation (33;38). Fat cell size and maturity are also related to leptin levels in the blood (35;36).

Growth hormone (GH) administration has been shown to impair insulin sensitivity under various conditions (39-41). Produced by the anterior pituitary gland, GH stimulates the growth of lean body mass and reduction of body fat mass (42;43). It plays a role in the development of insulin resistance at puberty to promote growth and is associated with insulin resistance and diabetes in individuals with excess GH secretion. Conversely, GH deficient individuals (43) and animals (44) have lower lean body mass, are obese, and exhibit increased circulating insulin levels and insulin resistance (45;46). GH declines with age (47;48) and energy restriction (47;49), and increases with overfeeding and growth (49;50).

Some research has been performed examining the various relationships between high-fat diets, obesity, glucose tolerance, growth hormone, and leptin. While animal studies examining the effects of intravenous glucose challenges on leptin secretion have been performed following dietary manipulation, we know of no studies utilizing oral glucose challenges, with the exception being our previous unpublished research, which utilized weanling rats though the development of sexual maturity. Most of the previous research has involved mature male rats (15;16;51-57). Results of this research will offer insight into the relationship between high-fat diets and the roles of leptin and growth hormone in the development of insulin resistance associated with increased fat mass and overweight in female rat models.

Therefore, the following research hypotheses were developed:

1. Rats fed high-fat diets will have greater total body mass and body fat content compared to rats isocalorically fed low-fat diets.
2. Rats fed high-fat diets will produce significantly higher leptin responses to oral glucose tolerance challenges compared to rats isocalorically fed low-fat diets during growth.
3. Rats fed high-fat diets will develop insulin resistance, evidenced by amplified insulin responses to oral glucose tolerance tests, compared to isocalorically low-fat fed rats.
4. Growth hormone concentrations of rats fed high-fat diets will not be different from growth hormone concentrations of rats isocalorically fed low-fat diets.

Based on the hypotheses, the following research objectives were developed:

1. To determine the effects of dietary fat content on growth (weight gain) and adiposity (% body fat) in rats isocalorically fed diets that have high or low fat content.
2. To determine the effects of dietary fat content on glucose, insulin, leptin and growth hormone responses to oral glucose tolerance tests over time.

Limitations

This study was designed to evaluate the effects of high-fat feeding during rapid growth in female rats. Due to limited resources, we were not able to examine rats younger than 56 days of age. The animals are too small before this age to withstand the procedures involved in this study. This study is also limited to female SD rats. Results of this research cannot be directly extrapolated to humans. Therefore, human research is also indicated to examine if similar physiological responses occur.

Thesis Format

This thesis contains five chapters: the introduction, literature review, methodology, results in the form of a journal article, and a summary, conclusions and recommendation section. The bibliography and journal article are written in the format required by Diabetes, the journal of the American Diabetes Association.

CHAPTER II

REVIEW OF LITERATURE

Obesity and Type 2 Diabetes Mellitus

Overweight and obesity are growing problems in industrialized nations such as the United States. National health initiatives such as Healthy People 2010 and the Dietary Guidelines for Americans recommend balancing physical activity with a diet of appropriate calories and less than 30% of energy from fat to maintain body mass index (BMI) associated with low rates of morbidity and mortality (9).

Obesity is highly associated with insulin resistance and the development of type 2 diabetes mellitus (DM). BMI positively correlates with the degree of insulin resistance in obese probands, as does waist circumference (2). Weight loss attenuates hyperglycemia, hyperinsulinemia, hypertension, and blood lipid parameters, indicating that excess weight is a contributing factor in the development of such metabolic aberrations. A 28-day diet and exercise intervention to reduce weight in obese men (BMI 32.1 ± 3.9 at baseline, 30.7 ± 3.9 at conclusion, $p < 0.001$) with untreated type 2 DM resulted in improved blood glucose (10.2 ± 3.3 to 6.8 ±2.2 mmol/ L). Serum insulin levels were also significantly reduced after the intervention, though values were within reference range at baseline (3). Reference fasting serum insulin values are 1-20 μU/ mL (6). Subjects' blood lipid profiles also improved significantly.

Overt DM is a failure to produce adequate insulin to maintain optimal blood glucose levels. Classic clinical symptoms of overt DM include hyperphagia, polydypsia,

polyuria, and weight loss. Currently, DM is classified into two categories: type 1 DM, in which the pancreas does not produce normal levels of insulin, if any at all, and type 2 DM, in which there is a relative deficiency of insulin to maintain normal blood glucose levels. When untreated, type 2 DM can progress to pancreatic fatigue and reduced insulin production (10). Roughly 10 to 20% of DM cases are type 1 which is the result of autoimmune-mediated destruction of the pancreatic beta cells. The remaining 80 to 90% of cases are of type 2, which may be caused by insulin secretory defects, and resistance of the hepatic and peripheral cells to insulin, resulting in a relative deficiency of insulin to maintain normal blood glucose concentrations (6).

Current criteria for the diagnosis of DM are:

- Fasting (8 + hours) serum glucose ≥ 126 mg/dL (7.0 mmol/ L), or
- Random blood glucose concentration ≥ 200 mg/dL (7.8 mmol/ L) with classical symptoms, or
- Fasting blood glucose ≥ 126 mg/ dL (7.0 mmol/ L) results in a provisional DM diagnosis.
- . All of the above findings must be confirmed on another day.
- Two-hour blood glucose concentration ≥ 200 mg/dl (7.8 mmol/ L) following a 75 g oral glucose load.

Based on these criteria, it is estimated that diagnosis occurs an average of six and a half years after DM has developed (58). Obesity is present in ~80% of type 2 DM patients at the time of diagnosis (10).

In addition to impaired glucose metabolism, patients with poorly controlled DM have altered lipid metabolism, micro- and macro-vascular changes which frequently lead

to hypertension, an increased risk of heart disease, blindness due to retinopathy, renal failure, and amputations. Individuals with type 2 DM are significantly more obese, dyslipidemic, and hypertensive than age- and gender-matched controls (5). In a study of Chinese patients with type 2 DM, more than 20% were centrally obese, and nearly half were generally obese. Of the obese patients with type 2 DM, 6% were hypertensive, 23% had dyslipidemia, and 27% had increased albuminuria (4). Initiation and continuation of DM treatment generally results in a rapid and prolonged decrease in total and LDL cholesterol, an increase in HDL cholesterol, and a mild reduction of plasma triglycerides in type 2 DM patients (59).

In the development of overt type 2 DM, there are two possible conditions of aberrant glucose tolerance that may be diagnosed prior to absolute DM, which are both classified as Pre-diabetes (60). Impaired Glucose Tolerance may be diagnosed if fasting glucose is ≥ 110 but < 126 mg/dl (6.0 to 7.0 mmol/ L), and the two-hour blood glucose value is ≥ 140 but < 200 mg/dl (7.8 to 11.1 mmol/ L), following a 75 g oral glucose load. Impaired Fasting Glucose may be diagnosed if either the fasting or two-hour glucose concentrations are within the ranges for fasting or two-hour post-load listed for Impaired Glucose Tolerance, but not both. These conditions are frequently asymptomatic, and aberrations in glucose tolerance may not be diagnosed until overt clinical symptoms develop (6;10).

The transition from impaired fasting glucose to impaired glucose tolerance and the development of overt type 2 DM is progressive, as evidenced by the UK Prospective Diabetes Study. Of over five thousand adult patients with type 2 DM studied for the first nine years following diagnosis, the proportion of patients receiving various treatments

(diet, insulin, sulfonylurea, or metformin) who were able to achieve glycosylated hemoglobin < 7.0% and fasting plasma glucose concentrations of < 7.8 mmol/ L decreased after three, six, and nine years of treatment, regardless of therapy. These results include both overweight and normal weight patients, although the attainment of blood glucose control was generally lower in overweight patients than in the entire cohort. Therapies evaluated included insulin, oral hypoglycemic agents (OHA), diet, or a combination of treatments (5).

Effects of high-fat diet on Glucose Tolerance and Insulin Resistance

In human studies, the effects of high-fat diets have been inconsistent and in conflict with epidemiological data. This may be due to many factors involved in the response to glucose loading, which are not similarly controlled between studies. Short term feeding of high-fat diets in humans does not seem to cause insulin resistance. However, in these studies, researchers did not consider the subjects' usual diets as an influence on their responses to glucose tolerance tests. Gender seemed to have an effect on insulin secretion in response to a single HF meal (79% of calories from fat) in one study. Mean serum insulin levels of women were not different postprandially compared to fasting levels while men's plasma insulin levels were significantly higher one hour after the meal compared to fasting. In both men and women, insulin levels following the high-fat meal were significantly lower than after a eucaloric LF meal (1% of calories). This reflects a decreased physiologic need for insulin due to decreased carbohydrate entering the body (61).

Following thee weeks of diet treatment, fasting and non-fasting glucose and

insulin levels were not different between HF or LF overfed healthy young men. This indicates that length of exposure to HF diets is a factor in the development of impaired glucose tolerance in humans (62). In eight healthy male and female volunteers, no significant differences in baseline insulin or glucose levels, or in the glucose infusion rate required to maintain euglycemia were found after thee weeks of randomized high-fat (≥ 45% calories from predominantly saturated fat) or low-fat (>30% of calories from fat) diet treatment. Time is a factor in the development of insulin resistance (63).

In animal models, evidence of impaired glucose tolerance due to high-fat feeding is mixed due to varied experimental designs utilizing different feeding durations, animal models, population samples, and dietary fat sources and content. A comprehensive table of rodent studies describing the rodent model, treatment diets, and method of insulin sensitivity evaluation is found in Appendix A. Research in dogs demonstrated that the consumption of diets containing 80% of calories from fat resulted in elevated fasting levels of both glucose and insulin compared to concentration when dogs were fed low-fat chow diets (14). Insulin sensitivity was decreased, as demonstrated by a lower rate of glucose disappearance after the dogs were fed the HF diets for 7 weeks. In this study, blood was sampled 44 times over a 24-h period in which animals had free access to food and water. When fed the HF diet, 24-h mean glucose concentrations and mean time-weighted average 24-h insulin concentrations were lower compared to when the dogs were fed chow. As would be expected, lower carbohydrate and higher fat intakes require a reduced amount of insulin due to the reduced carbohydrate-stimulated blood glucose increases.

Research in rats examining the effects of HF feeding on glucose and insulin

concentrations is equivocal. Several researchers have not found differences in fasting insulin and glucose levels between rats fed high and low levels of dietary fat for thee or more weeks (32;52;56;62). Other researchers have demonstrated that feeding rats HF diets for the same period of time results in increased fasting glucose concentrations, but not fasting insulin concentrations (13;16;17). Rats fed very HF diets (90.7%) for ten days had significantly higher serum glucose and insulin levels compared to chow-fed controls (146.5 ± 3.1 vs. 126.3 ± 3.5 mg/dl, and 10.2 ± 1.9 vs. 1.7 ± .3 ng/ml, respectively) (15).

Mice exhibit impaired glucose tolerance and insulin sensitivity in response to high-fat feeding. After 1.5 years of diet treatment (58% of kcal from fat), in both C57BL/6J (from which the *ob/ob* mouse originated) and NMRI strains of mice, fasting glucose levels were elevated only in HF C57BL/6J mice over controls of the same strain. Plasma concentrations of insulin at necropsy were greater in HF mice compared to chow fed animals of both strains. Intraperitoneal glucose tolerance tests in these mice demonstrated that HF feeding results in an increased area under the two-hour glucose curve in HF animals compared to LF animals (64). These same effects were observed following shorter durations of HF diet treatment (21).

Similar responses have been observed in rats. After feeding rats treatment diets for thee weeks, some researchers have not found differences in acute insulin responses to low-dose (300 mg/ BW_{kg} or 500 mg/ BW_{kg}) intravenous glucose administration following a fast. However, HF animals exhibited increased blood glucose levels over LF animals (51;56). Kraegen, Clark, and colleagues (51) did not find any differences in insulin and glucose concentrations between HF and LF animals after thee days or thee weeks of diet treatment. Levy and colleagues (52) administered a larger glucose bolus

(6.8 g/ BW_{kg}) and found no differences in glucose or insulin measures between HF and LF rats at 2, 3, 4, or 6 h after the challenge.

In an insulin tolerance study, researchers injected adult male rats, fed HF diets (39% kcal) for twelve weeks, with .125 U/ BW_{kg} insulin after measuring fasting blood glucose, then monitored blood glucose concentrations at 15, 30, 60, 120, and 180 min after the injection. Results demonstrated that animals fed HF diets had delayed BG responses to the injection. HF rats had significantly higher glucose levels 15 and 30 min after the injection, and significantly higher overall BG concentrations for the thee h following the insulin injection, compared to the LF rats (55).

Glycemic clamp studies are an excellent tool for assessing insulin sensitivity and glucose tolerance. In theory, by elevating the level of circulating insulin in animals, hepatic glucose production is inhibited. Researchers can then measure the amount of glucose required to maintain euglycemia. Researchers can determine insulin's ability to promote glucose disposal from the blood, presumably into muscle cells. This is referred to as whole-body glucose tolerance or insulin sensitivity (65). The hyperinsulinemic clamp is the most accurate method to measure insulin resistance.

After 24 ± 1 days of HF feeding, rats fed 59% of calories from fat had similar basal glucose and insulin levels compared to control-fed animals. HF animals required a significantly lower rate of glucose infusion to maintain euglycemia during a mid-physiologic range clamp study (54). In another study,

after feeding 60% of calories from fat for four weeks to the same strain of rat, however, basal levels of glucose and insulin were higher in treatment animals than controls. In addition, HF animals required a decreased rate of glucose infusion to

maintain euglycemia (17).

In hyperinsulinemic, euglycemic clamp studies, researchers found a significantly lower glucose infusion rate required to maintain euglycemia in rats fed HF in rats fed HF diets (59% of kcal) at three days and three weeks of diet treatment. Impaired insulin sensitivity worsened with the duration of feeding. Compared to rats fed HF diets for thee days, rats fed the HF diet for thee weeks required an even lower rate of glucose infusion compared to controls to maintain euglycemia (51). Similar results have been observed by other researchers (16;66;67).

Impairment of insulin-stimulated glucose uptake in muscle develops with duration of HF feeding. After thee days (51) to two weeks (68) of diet treatment, muscle glucose uptake was not different between HF and control animals. After four weeks or more of HF diet treatment, insulin-stimulated glucose uptake into muscle was significantly lower than either control animals or when compared to uptake before HF diets were initiated (32;54).

Effect of high-fat feeding on body weight and body fat

Studies examining the effects of high-fat feeding on body weight gain in rats show varied results. This may be due to the effects of rat strain, gender or age, feeding duration, changes in consumption, or type or quantity of fat in the treatment diets. Researchers found no differences in body weight post-intervention in rats fed between 36% and 90.7% of calories from fat and control-fed rats on low-fat refined or chow diets (15;16;52;54;56;66;68-70). In contrast, other researchers have found that adult obesity-prone and obesity-resistant, as well as young rats, weighed significantly more than

controls after five to six weeks of high-fat feeding (45% to 65% of calories from fat) (13;32).

Two strains of mice fed a high-fat diet for 1.5 years weighed significantly more than chow-fed controls, which is consistent with rat and dog models (14;64).

Though HF feeding has not consistently resulted in greater body weight gain in rats compared to LF controls, in most studies greater than thee weeks' duration, HF animals had a higher percentage of body weight as fat and had greater visceral fat mass (13;16;17;52;54;68-70). In rats provided a choice between HF or LF energy sources, energy intake and body weight of fat preferring rats were not different from carbohydrate preferring animals in one study (41). In a similar study, body weight of fat-preferring rats was higher than carbohydrate-preferring animals, despite similar mean daily energy intake. These researchers attributed the increased body weight to high energy consumption and weight gain in the HF animals during the first ten days of feeding compared to high-carbohydrate fed animals (71).

Magnetic resonance imaging (MRI) of female mice fed a HF diet (58% kcal) for ten months revealed significantly higher visceral and subcutaneous abdominal fat depots than in LF controls (21). Weight gain from consuming HF diets is attributable to an increase in body fat mass, and not to an increase in lean mass (14).

Effect of high-fat feeding on food intake

Researchers have observed an initial increase in energy and food consumption when rats are fed diets high in fat (41;71). These findings are not entirely consistent. HF fed rats consuming 66.5% of calories as fat did not differ in total caloric intake from low-

fat fed controls over a thee week experimental period (66). Both obesity-prone (OP) and obesity-resistant (OR) rats fed ad libitum HF diets consumed significantly more calories during the first week of diet treatment than LF controls. After five weeks of diet treatment, both OP and OR high-fat fed rats consumed more cumulative energy. In this study, OP rats consumed greater total energy than OR rats on the same high-fat diet, indicating that genetics is a co-factor in feeding experiments (13).

Effect of fatty acid composition

The fatty acid composition of the diet has an impact on the development of impaired insulin sensitivity. In one study, animals fed saturated fat required the lowest rate of glucose infusion during a glycemic clamp study, while those fed either PUFA with long-chain n-3 fatty acids or saturated fat with shorter-chain n-3 fatty acids (16 carbons) required the highest rate of glucose infusion to maintain euglycemia. Although animals fed a diet of PUFA alone as the fat source did not significantly differ in insulin sensitivity from those fed the saturated fat diet, the MUFA-based diet, or the PUFA with 16-carbon n-3 fatty acids, they did require significantly less glucose to maintain euglycemia than animals fed either the PUFA plus long-chain n-3 or the saturated fat plus 16-carbon n-3 fatty acids (53).

Caloric restriction of high-fat fed animals resulted in significantly decreased insulin levels for rats fed both safflower oil- and fish-oil-based diets, while those fed a beef tallow-based diet demonstrated a mild, nonsignificant increase in circulating insulin levels (72). The level of incorporation of n-3 fatty acids into the phospholipid portion of muscle membranes has been linked to maintenance of muscle insulin sensitivity. Rats fed

diets high in polyunsaturated fats with the addition of fish oil, which is rich in the n-3 eicosapentanoic and docosahexanoic fatty acids, maintained muscle insulin sensitivity. The addition of linseed (flax) oil, rich in α-linolenic acid, does not demonstrate the same protective effect. Linseed oil does, however, exert a protective effect against insulin resistance when added to diets high in saturated fat. These results indicate that the ratio of n-6 to n-3 fatty acids in the diet is more important than the total amount of dietary fat consumed in affecting glucose tolerance and insulin sensitivity (53).

Insulin sensitivity in humans, as a result of consuming high-fat diets, appears to depend on the total amount of energy provided by dietary fat rather than the source of dietary fat or the duration of feeding. Among individuals consuming less than 37% of energy from fat as determined by food records, those consuming a greater proportion of saturated fat (SFA) had reduced insulin sensitivity following ninety days of diet than subjects consuming primarily monounsaturated fat (MUFA) (-12.5% vs. +8.8% respectively), as demonstrated by intravenous glucose tolerance testing. Among subjects consuming greater than 37% of energy from fat, both SFA and MUFA intakes were comparable, lending explanation to the lack of difference in insulin sensitivity between the SFA fat group and the MUFA group (73).

Introduction to Leptin

In 1973, Coleman (74) described experiments with *ob* and *db* mice, which appear very similar. Both animals are obese, have diabetes, and have markedly increased concentrations of insulin in the blood. Both are descended from the same genetic strain, the C57BL/6J mouse. When *db/db* mice were pararabiosed with non-mutated mice, the

normal mice stopped eating, lost weight, and soon died. When *ob/ob* mice were parabiosed with normal mice, both animals of each pair gained weight, and pairs lived until the time of necropsy several months later.

When *ob/ob* and *db/db* mice were parabiosed to one another, of the 16 pairs joined, only one pair survived until the scheduled necropsy four months later. Median survival time for parabiosed *ob/ob* to *db/db* pairs was 26 days. The *db/db* mice remained diabetic and obese. They continued to gain weight, had food-engorged stomachs at necropsy, and were extremely obese. Conversely, the *ob/ob* mice all lost approximately 15 g, were severely hypoglycemic, and had virtually stopped eating, as they had very little food in their gastrointestinal tracts at autopsy (74).

Because of the similarity in responses between normal and ob/ob mice to parabiosis with db/db mice, Coleman proposed that a "satiety factor" was at the center of the phenomena. He suggested that db/db mice produce the factor, but do not respond to it, and that ob/ob mice have functional "satiety centers" but lack the satiety signal (74).

It was not until 1994 that the satiety factor Coleman suggested was identified and named leptin.

Leptin

Source and secretion

Leptin, first identified in 1994 by Zhang et al (75), is a 16-kDa peptide hormone produced in and secreted by adipocytes. In human beings, the serum leptin reference value of 1 – 16 μg/ L is based on the analysis of leptin concentrations of individuals with

body fat percentages considered to be optimal, which is ≤ 15% body fat for men and ≤ 25% body fat for women (6). The reference range for leptin concentrations in rats is 1 – 7.7 μg/ L (Linco, St. Louis, MO).

Leptin secretion follows a diurnal rhythm, with highest levels in the blood during sleeping hours (18). This pattern is evident in obese and lean humans, including those with DM (19). Studies have demonstrated that leptin secretion is pulsatile in nature, with pulses occurring approximately every thirty minutes (18;37).

Leptin is believed to be secreted in response to insulin in the blood. Hyperinsulinemic euglycemic clamp studies performed on fasted overweight healthy men demonstrated that plasma leptin concentrations increased positively in relationship to the insulin infusion concentration. However, this study also employed glucose infusions to maintain euglycemia, which precludes conclusion that insulin alone stimulates leptin release (76). In vitro studies of an adipocyte cell line revealed that leptin is produced by mature fat cells. Leptin mRNA production is stimulated by the addition of insulin to the culture media, and suppressed by the insulin removal, as is leptin release from the mature adipocytes (23). Isolated rat adipose cells cultured with insulin secreted and retained more leptin than cells of the same animals cultured without insulin (24). Taken together, these in vitro results indicate that insulin indeed stimulates leptin production and release by adipocytes.

Circulating leptin levels reflect body fat stores in the well-nourished state. Serum leptin levels were significantly higher in obese hyperinsulinemic women as compared to non-obese, non-hyperinsulinemic controls (34). Obese men with untreated type 2 DM who underwent exercise training and caloric restriction demonstrated significantly

reduced serum leptin levels after a four-week intervention period. Correlation was found between BMI and serum leptin at baseline, but was not evaluated at the end of the intervention (3). A significant positive correlation exists between fasting serum leptin levels and BMI in obese and normal-weight women, and in Asian Indian men and women (33;34).

Researchers have determined a direct linear relationship between circulating leptin levels and body weight in mice, although the slope of this relationship varies with animal strain (64). Correlational analysis reveals that log serum leptin positively correlates with body weight and body fatness regardless of diet treatment (21). Gold thioglucose-obese mice, characterized by extreme adiposity, had significantly higher serum leptin levels than lean controls at ten weeks of ad libitum feeding (44.7 ± 3.4 vs. 16.0 ± 1.0 ng/ml, respectively) (77;78). Leptin levels in male Fischer-344xBN rats were significantly correlated with multiple fat depot weights at 3, 24, and 31 months of age (78).

Leptin levels also correlated significantly to the Lee index, a mathematical indicator of body adiposity in rodents ($r = .92$-$.96$ for ages 3 to 31 months, $P < .001$). (78). In a study of lean and obese female Wistar rats, leptin levels were significantly higher in obese animals than in their lean littermates (28).

Leptin gene expression appears to be dependent on the maturity and location of the adipose cells. Researchers determined that isolated mature human adipose cells had significantly higher leptin mRNA than was determined in adipose tissue which contained both mature and immature cells, and that subcutaneous fat cells express significantly more leptin mRNA than those from visceral stores (35). In all subjects of one study, leptin mRNA levels were significantly higher in subcutaneous adipose tissue than in

visceral stores (36).

Gender may also be an independent predictor of leptin in the blood. In infants twelve months of age and younger, girls had higher plasma leptin levels than boys, even after correction for BMI (37). Boys' and girls' serum leptin concentrations reflected the same dichotomy at similar body weights from ages 5 though 15 (38). Analysis by bioelectrical impedance analysis and DXA confirm that women have higher circulating leptin levels than men at equal BMI, body weight, body fat mass, and body fat percent (33). This could be associated with the finding that women have a higher mean ratio of subcutaneous-to-omental fat than men (36).

Some researchers have identified a relationship between age and leptin levels in the blood, although the significance of this relationship is unclear, except in species known to increase in adiposity with age, such as rats. Age was a predictor of leptin levels in babies only between one and six months of age (20). In children between five and fifteen years of age, girls exhibited a steady increase in serum leptin levels with age. Boys demonstrated an increase in serum leptin concentrations until age ten, after which levels fall steadily (38). Age was not correlated significantly with leptin in adult men and women (33). Fischer 344xBN rats' serum leptin levels were significantly increased with age, from 3 to 24 to 31 months of age (78).

Leptin's relationship with age in young mammals may be related to its role in sexual maturation. In young girls, serum leptin concentrations rise steadily from prepuberty though mid-adolescence and the onset of reproductive function. The rise in leptin levels is similar in boys, until testosterone levels begin to increase, at which time leptin concentrations begin to steadily decline (38).

Although leptin reflects adiposity, this reflection is disrupted with fasting and negative energy balance. In male rats fasted for 48 h with access to water, serum leptin levels and body weight declined significantly as compared to controls maintained with ad libitum feeding (78). Obese men with untreated type 2 DM who underwent weight loss though exercise training and caloric restriction demonstrated significantly reduced serum leptin levels after a four-week intervention period (3).

Leptin inhibits the secretion of hypothalamic neuropeptide Y, an appetite stimulant, in the brain. Fasted female mice exhibited decreased leptin levels following a 48-h fast, as compared to non-fasted control mice (21). This effect was also evident in healthy adult women in the first day of a four-day fast (79).

Previously, HF diets were shown to increase body fatness. Expressed as a percentage of eviscerated carcass weight, researchers determined there was a direct relationship between serum leptin levels and body fatness in rats after HF feeding (57). Fish oil- and safflower oil-fed rats had significantly higher circulating leptin concentrations and smaller perirenal fat mass and cell size than animals fed a beef tallow-based diet which provided the same amount of energy and fat. When energy intake was decreased to 85% of ad libitum by removal of carbohydrate from the diet, leptin levels decreased in animals on both the fish oil and safflower oil diets to concentrations comparable to ad libitum-fed rats on the saturated fat diet, but not in those rats fed the tallow-based diet (72).

The effects of HF feeding on leptin levels in the blood are also inconsistent from study to study. Two separate experiments by the same researchers indicate an immediate effect of diet on serum leptin levels in mice, with significantly greater areas under the

curve for both the first and second days of high-fat diet treatment as compared to low-fat fed controls (134.6 ± 10.3 vs. 100.0 ± 12.3, P = .028 for day one, and 126.5 ± 8.2 vs. 100.0 ± 5.2, P + .016 for day two) (80). While some researchers found significantly increased fasting leptin levels in HF rats (15;32), others found no differences in either fasting levels of leptin or in leptin responses to IVGTT following a 6.8 g/kg BW glucose load versus controls (52). Other researchers have found similarly inconsistent results in non-fasted rats. HF rats fed both ad libitum and at a restricted-calorie level had significantly higher serum leptin levels than ad libitum chow-fed controls (68). Steinberg and Dyck found that HF rats had higher serum leptin levels than controls after four weeks (70), as did others after only ten days of feeding (15). Researchers have also found significantly higher plasma leptin levels after four weeks of HF feeding, but this effect did not persist to fourteen weeks of diet treatment (69). When normalized per gram of body fat, HF rats had significantly greater leptin levels than LF rats in one study (70), but the reverse was found in another (69).

Leptin serves as a messenger to the brain from the adipose cells, indicating energy balance. Within the brain, leptin binds receptors in the ventromedial hypothalamus, thereby inhibiting production of neuropeptide Y, a polypeptide known to stimulate appetite. In male rats fasted 48 h, serum leptin levels and body weight declined significantly, and hypothalamic neuropeptide Y mRNA levels significantly increased as compared to controls maintained with ad libitum feeding, an expected result given the relationship between leptin, body weight, and neuropeptide Y (78).

Leptin has been linked with postprandial satiety and subsequent meal intake. In the postprandial period, leptin levels increase, then decline somewhat in most subjects,

triggering an increase in hunger and soon followed by the request for the next meal in subjects fed ad libitum and deprived of time cues. Leptin levels at the time of meal onset, however, are not associated with energy intake at the meal (37). Animal research indicates that administration of leptin to both female and male rats reduces 24-h energy intake up to 20% by reducing meal size (29;30). Researchers demonstrated that intracerebroventricular leptin injection significantly inhibits food intake in rats by injecting 0.4, 1.0, and 4.0 μg of murine leptin and observing total food intake for the following 22 h. Reductions in food intake, as compared to vehicle-injected controls, increased as dose increased (15%, 26%, and 40% reductions in intake for 0.4, 1.0, and 4.0 μg doses, respectively), though the linearity of the relationship was not evaluated (31). Intraperitoneal injection of 1 mg leptin reduced rats' food intake by 26% as compared to control rats over the 22 h following the injection (31).

Moderate hyperleptinemia in rats, induced by injection of a recombinant adenovirus containing rat leptin cDNA significantly decreases ad libitum caloric intake in both high-fat fed and chow-fed animals versus non-treated controls on the same diets (42.61 ± 2.7 kcal/d vs. 93.3 ± 0.9 and 35.45 ± 1.6 vs. 95.9 ± 0.6, respectively). Induced hyperleptinemia decreases caloric intake significantly more in chow-fed rats than HF rats (32). Weight loss was marked in chow-fed hyperleptinemic animals as compared to chow-fed, calorie-matched, non-hyperleptinemic rats injected with a adenovirus that does not affect leptin production. Weight loss in high-fat fed hyperleptinemic rats was not significant compared to non-hyperleptinemic high-fat fed animals (32).

In an attempt to minimize the appetite-suppressing effects of leptin administration, researchers injected high-fat fed rats daily with a 1 mg/ BW_{kg} dose of

leptin at the beginning of the light cycle, and found that weight was reduced by 8% after four days of hormone administration as compared to high-fat fed, non-leptin treated animals (68).

Hyperleptinemia produces significantly greater visceral fat mass reductions in HF rats than in calorie-matched, non-hyperleptinemic animals fed the same diet well as hyperleptinemic animals fed chow (44 ± 6 vs. 20 ± 2 and 40 ± 5, respectively). Rats treated with recombinant mouse leptin for eight days had significantly decreased visceral fat mass (pooled epididymal, perirenal, and mesenteric fat pads) compared to control rats (32). Similar decreases were observed in rats subjected to caloric restriction for the same period of time. In addition, leptin-treated and caloric-restricted rats demonstrated a significantly decreased rate of glycogenolysis compared to controls (81).

The ratio of fatty acid (oleate) esterification to oxidation in both soleus and extensor digitorum longus muscle was significantly reduced by treatment with leptin as compared to both insulin-treated and untreated muscles of the same type, and compared to muscle fibers treated with both insulin and leptin (82). In isolated muscle cells from *ob/ob* mice and their lean littermates, leptin treatment increased radiolabeled fatty acid (oleate) oxidation significantly compared to non-treated contralateral muscles (15% to 30%), and decreased the incorporation of fatty acid into triacylglycerol by as much as 30%. Treating muscles simultaneously with leptin and insulin resulted in a net cancellation of insulin's fat-storing effects (82).

Researchers found no significant differences in either exogenous palmitate oxidation or esterification into triglyceride between high fat fed or control animals' muscle fibers treated with leptin. However, leptin-treated muscle fibers of low-fat fed

animals exhibited a significantly higher mean exogenous palmitate oxidation rate compared to untreated soleus muscle fibers of the same treatment group (70).

A possible explanation exists for the seeming failure of leptin to inhibit appetite in obesity, whether genetic or diet-induced. Human and animal research indicates leptin transport mechanisms at the blood-brain barrier are easily saturated. High-fat fed lean Zucker FA/FA and energy-restricted genetically obese Zucker fa/fa rats had similar levels of radio-iodinated leptin in all regions of the brain following radiolabeled leptin injection into the branchial vein. Despite similar levels of leptin in cerebrospinal fluid, these levels were significantly lower than those found in lean, low-fat fed Zucker FA/FA rats (83). In an experiment to mimic leptin transport at the blood-brain barrier, isolated human brain capillaries incubated for 120 min with iodinated leptin and then acid-washed demonstrated significant leptin incorporation into the endothelial membrane, which persistently increased over the incubation period at 37°C. Brain capillary plasma membranes incubated similarly and in the presence of insulin, exhibited binding and incorporation into the membrane which appeared to be saturable as leptin concentration in the media increased, and was not affected by the presence of insulin (84).

Researchers found that obese individuals with a mean serum leptin concentration that was 318% higher than normal-weight subjects had only 30% higher concentrations of leptin in cerebro-spinal fluid (CSF), another possible explanation for the seeming resistance to hyperleptinemia in obesity (85).

Gold thioglucose-injected obese mice demonstrated significantly reduced serum glucose and insulin levels two-hours after a 25 μg intraperitoneal injection of recombinant mouse leptin, as compared to lean leptin-treated and gold thioglucose-

treated, leptin-untreated animals (77). In a study using pancreatic INS-1 insulinoma cells, researchers found that leptin concentrations of 20 nmol/l had no influence on insulin release in response to 10 mmol/l glucose stimulation in relation to cells not exposed to leptin. Similar results were found at a non-stimulatory glucose concentration of 3 mmol/l in conjunction with leptin concentrations ranging from .5 to 50 nmol/l. These researchers also found that in the presence of agents that raise intracellular levels of cAMP, leptin does inhibit the secretion of insulin in response to glucose (25).

There is relationship between endogenous leptin levels in the blood and insulin resistance or sensitivity. Researchers found a significant positive correlation between degree of insulin resistance and circulating leptin levels in a study of 22 lean and obese insulin sensitive (IS) and insulin resistant (IR) subjects (2).

In rats subjected to intravenous glucose tolerance tests (IVGTT), leptin infusion decreased basal insulin and triglyceride levels in the blood, as well as significantly decreased the insulin response to the glucose bolus (27). Leptin infusion at rates of 0.1, 0.5, and 5 μg/ BW_{kg}^{-1}/ minute during a hyperinsulinemic, euglycemic clamp study in rats produced rapid decreases in plasma insulin levels. The dose-response relationship between leptin and insulin was significant at $r = -0.731$ (25).

Cultured rat hepatocytes and adipocytes treated with leptin exhibited significantly reduced insulin binding as compared to untreated cells, demonstrating that leptin inhibits insulin binding at the cellular level (28).

Adipocytes cultured in 50 nM of leptin bound 19% less ^{125}I-labeled insulin than non-leptin treated cells, and binding was reduced by 24% compared to untreated cells at leptin concentrations of 2.5 μM in culture (26). Leptin concentrations of 20 nmol/ L did

not inhibit glucose-stimulated insulin release from cultured pancreatic INS-1 β-cells, but did inhibit insulin release stimulated by other hormones (25). In isolated mouse muscle fibers, leptin induced fatty acid oxidation prevented by insulin in leptin's absence (82). In the absence of insulin, leptin had no effect on cellular metabolism in culture, but did inhibit insulin-mediated glucose metabolism and lipogenesis and stimulate lipolysis in insulin-stimulated conditions (86).

Rats treated with daily 1 mg/ BW_{kg} injections of leptin for four days at the end of a 28-day high-fat feeding trial exhibited significantly reduced insulin-stimulated muscle glucose uptake as compared to control chow-fed rats, but significantly greater uptake as compared to rats on the same high-fat (50% of calories) (68).

Both high-fat- and chow-fed rats treated with a recombinant adenovirus to produce moderate hyperleptinemia exhibited significant decreases in plasma glucose and insulin levels as compared to HF, calorie-matched (to high-fat, hyperleptinemic rats) animals treated with a control adenovirus (glucose levels 135.7 ± 6.7 and 112.25 ± 12.5 mg/dl respectively, vs. 156.5 ± 5.5 mg/dl, $P < .05$, and insulin levels .64 ± .21 and .23 ± .1 ng/ml vs. 3.79 ± .7 ng/ml) (32).

Eight days of recombinant mouse leptin administration to male rats resulted in decreased food intake, which was associated with improved fasting glucose tolerance and insulin sensitivity, as evidenced by significantly lower fasting insulin levels but similar fasting glucose levels in leptin-treated rats as compared to untreated control rats and calorie-restricted rats that lost a similar amount of weight. Hyperinsulinemic, euglycemic clamp results indicate that leptin-treated rats' insulin-stimulated glucose uptake was significantly higher (63%, $P < .001$) than that of controls and calorie-restricted rats that

had lost similar amounts of visceral fat. This increase in glucose uptake is attributable to both increased glycogenesis and glycolysis (81).

Growth Hormone and Insulin Resistance

Growth Hormone (GH) is produced and released from the pituitary gland within the mammalian brain. Its production is stimulated by Growth Hormone Releasing Hormone, which is produced in and secreted from the hypothalamus (87). GH stimulates growth of lean body mass (42). Deficiency results in excess body fat accumulation (88), while excess stimulates hypertrophy and hyperplasia (50). GH concentrations in the blood exhibit a circadian rhythm, with elderly individuals demonstrating peak GH concentrations during late waking hours, and younger probands exhibiting peak concentrations during sleeping hours (48). In female rat pups, median GH secretion is high, and median plasma GH levels fluctuate with aging, with concentration ranges within age exhibiting a wide range, and pulsatile secretion fluctuating every 2 to 4 hours (47). GH influences lipid metabolism at the tissues (89). Researchers found that exogenous GH administration increased both abdominal and femoral adipose interstitial glycerol, free fatty acid, and 3-OH-butyrate concentrations compared to saline administration. GH is associated with increased glucose-stimulated insulin secretion during puberty (90), and is inversely associated with pubertal insulin sensitivity (45).

Growth hormone administration in deficient subjects is associated with increases in lean body mass and reductions in body fat mass without significant changes in BMI. This shift in body composition is associated with decreased serum leptin levels and increased circulating insulin levels in both adults and children (43).

Exogenous GH treatment or endogenous GH excess results in impaired insulin sensitivity or insulin resistance. Acromegalic patients, who hypersecrete GH, hypersecrete insulin and exhibit impaired insulin sensitivity compared to normal weight, normal GH controls, but not when compared to weight-matched subjects, indicating a similarity in the metabolic changes of obesity and excess GH (50). In GH deficient children receiving GH treatment who developed IGT or type 2 DM, approximately one third of those who stopped GH treatment experienced improvements in glucose tolerance following cessation of GH treatment. Children between the ages of 6 and 19 years receiving GH treatment were also found to be at increased risk of developing type 2 DM (91).

Administration of a single bolus of exogenous GH in humans induces a significant acute increase in serum leptin concentrations within 24 h, followed by a significant decrease in leptin concentrations within 72 hours of the injection, without a change in body composition (17). Similarly, researchers found that two and a half days of twice daily injections of 1 gm/ Bw_{kg} GH in rats had no effect on fasting plasma glucose or glucose tolerance, but increased fasting plasma insulin levels by 65% and insulin response to a glucose load by 35%(90) (92).

The effect of administration of GH on insulin sensitive individuals without pre-existing metabolic conditions is equivocal. In young men, a single 200 μg intravenous injection of GH intended to mimic a physiologic pulse to produce an increase in serum GH did not produce any alterations in serum insulin, glucose, or glucagon over the ensuing 6 h (89). Growth hormone administration in normal subjects to achieve levels of 30 to 35 ng/mL did not change fasting insulin or glucose levels, but increased glucose-stimulated insulin secretion and reduced insulin sensitivity following an oral glucose

challenge (46).

Under non-hyperinsulinemic glycemic clamp conditions, GH infusion had no effect on plasma insulin and glucose in rats compared to controls receiving a saline infusion. When hyperinsulinemic euglycemia was induced following the elevation in GH for the subsequent 150 minutes, growth hormone infused rats required a significantly lower rate of glucose infusion to maintain euglycemia for 220 min and later. This decrease in insulin-stimulate glucose uptake reached 37% by 5 h after initiation of the GH infusion. In the already insulin-stimulated state, initiation of GH infusion resulted in a 32% decrease in insulin-stimulated glucose uptake, which reached significance 180 min after GH infusion began. This effect of GH infusion was due mainly to suppression of peripheral insulin sensitivity and not of hepatic glucose output (39).

Although a significant positive correlation did exist between GH concentrations in plasma and the degree of insulin resistance in one study, circulating GH levels of insulin resistant obese subjects (mean BMI 30.3 ± .8 kg/m^2) did not differ significantly from obese and non-obese insulin-sensitive controls (mean BMI 25.9 ± .3) (2).

Newly diagnosed obese/ overweight Chinese subjects with type 2 DM had significantly lower plasma GH concentrations than normal weight, nondiabetic controls. In this study, plasma growth hormone was significantly negatively correlated with waist circumference; this significance was eliminated when BMI was controlled for (4).

GH concentrations seem to be sensitive to negative energy balance in humans and rats. In adolescent wrestlers, intentional weight loss prevented an expected increase in GH secretion compared to non-weight-restricting controls. GH concentrations normalized when weight restriction ceased, and growth then increased, compensating for

the lack of growth during weight restriction (49). Rats fasted for 20 h exhibited suppressed GH peak secretion (47). In contrast to rats, hypoglycemia induced by hyperinsulinemic glucose clamp, resulted in significant increases in GH levels in men and women. Hypoglycemia, clamped at 70 mg/ dL, induced an 11-fold GH increase in men, and a nearly 4-fold increase in women compared to normal fasting glycemia (90 mg/ dL). Further decreases in blood glucose concentrations resulted in further increases in GH concentrations in both genders, with significantly greater GH levels in men than in women (93).

The effects of induced GH deficiency are not consistent between studies. In vivo GH administration by minipump produced significant reductions in basal glucose transport in adipocytes at 50 mU/ day with as little 12 h of infusion (40). Treatment with GH antiserum reduced growth hormone and insulin levels in vivo, as well as increased the in vitro rate of lipogenesis in adipose cells isolated from rats treated with the antiserum. When GH was administered to GH-depleted animals, these effects were reversed (94). Isolated adipocytes from GH deficient rats exhibited significantly increased glucose uptake and lipogenesis when incubated for 1 ,3, or 6 h with anti-rat GH serum as opposed to that of cells incubated with non-immune serum. When incubated in the presence of insulin, this increased glucose utilization persisted in antibody-treated cells, but was not enhanced by the addition of insulin more than in non-antibody-treated cells (95).

In summary, overweight and obesity are growing health concerns in industrialized nations such as the US, where caloric intake is increasing and physical activity is decreasing, especially among the young (9). Excess body weight and body fatness

contributes to health conditions such as heart disease, dyslipidemias, and type 2 diabetes mellitus.(96) High-fat diets providing excess energy contribute to increased body weight and body fat accumulation, impaired glucose tolerance and insulin resistance in laboratory animals and humans, but the mechanism by which this occurs is not clear (14;51;54;55;62;68). Body fat is positively correlated to leptin concentration, which is positively correlated to insulin resistance and negatively correlated to insulin-stimulated glucose uptake (21;22). Type 2 diabetes, characterized by insulin resistance and impaired glucose tolerance, frequently is not diagnosed until overt symptoms such as weight loss, increased appetite, and frequent urination develop (6).

Diets high in fat are known to increase body weight and fat mass, induce alterations in carbohydrate and lipid metabolism, lead to insulin resistance, and increase production and release of the hormone leptin in humans, rodents, and other animals (13-17).

Obese individuals produce twice the amount of leptin compared to slender individuals, and there is evidence indicating this is due to increased production of leptin by subcutaneous adipocytes compared to visceral fat cells (35;36).

This study examines the development of impaired insulin sensitivity in female rats fed high fat diets during rapid growth and sexual maturation.

CHAPTER III

MATERIALS AND METHODS

Animals

This research project was approved by the Institutional Animal Care and Use Committee of Oklahoma State University, Stillwater, under protocol number HE 01-16 (Appendix B).

Twenty female weanling Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) were randomly assigned to one of two diet treatments. Animals were 21 days of age on arrival, and were housed individually in hanging steel cages. Body weight (BW) in grams was recorded on arrival, and weekly thereafter. Animals were fed their assigned diets on the day of arrival and for the duration of the study. All animals had free access to deionized water and were kept on a 12:12 light: dark cycle (lights on at 0700).

Diet Treatments

Diet composition and energy value are outlined in Table 1. The diet treatments differed in fat and carbohydrate content. The LF diet contained 10% fat by weight, and the HF diet 20% fat by weight. Both diets were prepared to provide an equal amount of vitamins and minerals per calorie, and contained equal percentages of protein and fiber by weight. Energy requirements for young growing rats (3 to 7 weeks of age) is at least 227 kcal/ $BW_{kg}^{0.75}$ per day, while the energy consumption of mature (> 7 weeks of age) rats is calculated at 150 kcal/ $BW_{kg}^{0.75}$ per day (97). Based on a projected weight of 100 g at 5

weeks of age, the maximum expected energy requirement during the first 2 weeks of feeding trial was 40 kcal per day. Based on a projected BW of 250 g by the end of the study, maximal daily energy requirements for the animals were calculated to be 53 kcal per day. Animals were intentionally provided excess food energy during this study. For the first 2 weeks, animals received 53 ± 0.5 kcal (13 g LF diet and 11.7 g HF diet) per day. After 2 weeks of diet treatment, when at least half of the animals were consuming 100% of the food provided, the amount of diet was increased to 65 ± 0.5 kcal (15.85 g LF diet and 14.22 g HF diet) per day. Food intake was measured for 24 h preceding each DXA measurement for 3 or 4 animals in each treatment group.

Glucose Tolerance Tests

After 5 weeks ± 1 day of the feeding trial, when the rats were 8 weeks of age and had an average weight 166 g, an oral glucose tolerance test was performed on animals (OGTT #1) following an overnight fast. Free access to de-ionized drinking water was allowed during the fast. On the morning of the OGTT, animals were weighed, then approximately 1.0 mL of blood was collected via the tail vein. Blood glucose was determined using a DEX glucometer (Bayer Corporation, Elkhart, IN). Each animal was then gavaged with 2 g glucose/ BW_{kg}. The time at which the gavage was given was recorded as "Zero hour." One mL blood samples were then taken from the tail vein 30, 60, and 120 min after glucose administration. The first drop of blood at each collection time was used to determine blood glucose using the DEX. Blood samples were collected into polypropylene microcentrifuge tubes and kept on ice until processing. Glucose tolerance tests were repeated at two-week intervals, at 10 and 12 weeks of age (OGTT #2

and OGTT#3, respectively), with average weights 191 ± g and 211 ± g, respectively. The glucometer was calibrated on each day of glucose tolerance testing. The inter-assay coefficient of variation (CV) for glucose was 5%.

Dual X-ray Absorptiometry

At 6, 8, and 10 weeks of treatment (when 9, 11, and 13 weeks of age), animals were sedated with 58 mg/ BW_{kg} ketamine HCl and 2.9 mg/ BW_{kg} xylazine. A model 4500 Elite Dual X-ray Absorptiometry machine (DXA, Hologic, Waltham, MA) was then used to estimate body fat mass and lean body mass.

Necropsy, Blood and Tissue Collection

On the day of the final DXA scan, animals were necropsied following the scan, and exsanguinated via the abdominal aorta. Liver, heart, right soleus muscle, and fat were harvested and placed in labeled cryovials, then snap frozen in liquid nitrogen and stored at -80° C.

All blood samples were kept on ice for a minimum of 30 min before centrifugation (Jouan, Inc., model CR-3i) at 3300 x g for 15 min. Serum was aliquoted into labeled tubes. Serum insulin and leptin were determined by radioimunoassay (RIA, Linco Research, Inc., St. Charles, MO). Intra- and inter-assay coefficients of variation (CV) were 10.3% and 7.8% for insulin, 7.1% and 7.4% for leptin, respectively. All GH samples were analyzed in one assay, with an intra-assay CV of 7.0%.

Area under the curve was calculated for glucose, insulin, and leptin responses to each glucose tolerance test by summing the areas under each consecutive blood or serum

observation using the formula: $AUC = \frac{1}{2} \Sigma (t_{i+1} - t_i)(y_i + y_{i+1})$ (59)

Statistical Analysis

SAS Version 8 Statistical Analysis Software for Windows was used to analyze all data. Data outliers indentified by the Univariate procedure, which defines outliers as being greater than 1.5 interquartile ranges from the 25th to the 75th interquartile were excluded. The Mixed procedure was used to determine significant main effects and their interactions, with the Slice procedure used to determine differences between groups. Pearson correlation coefficients were determined using the Corr procedure. The level of significance (α) was set at $p \leq 0.05$.

Table 1. Composition and energy value of experimental diets.

	Low-fat diet	High-fat diet
	g/kg Diet	
Casein	200	200
Cornstarch	100	100
Sucrose	500	400
Cellulose	50	50
Soybean oil	100	200
Mineral mix*‡	35	39.3
Vitamin mix†‡	10	11.2
L-Cysteine	3	3
Choline Bitartrate	2	2
	% kcal	
CHO	58	43
Fat	22	39
Protein	20	17
	kcal/ g diet	
Energy Density	4.10	4.57

* Mineral mix composition is detailed in Appendix B.

† Teklad vitamin mix, catalog #40060.

‡ Amounts of mineral and vitamin mixes in the high-fat diet were adjusted to equal the amounts per calorie in the low-fat diet.

CHAPTER IV

EFFECT OF HIGH-FAT DIET ON BODY COMPOSITION AND HORMONE RESPONSES TO GLUCOSE TOLERANCE TESTS

Abstract

This study examines the effect of high-fat diet on glucose tolerance, blood glucose and insulin responses to a 2 g/ BW_{kg} oral glucose challenge, as well as the role of leptin in the development of insulin resistance. Growth hormone (GH) was measured to elucidate whether GH is involved in the development of diet-induced insulin resistance during growth. Twenty weanling female Sprague-Dawley rats were randomly assigned to a high-fat (HF, 39% of calories) and low-fat (LF, 22% of calories) diets. Oral glucose challenges were administered following 5, 7, and 9 weeks on the feeding trial. Animals were provided diet in excess of their requirements for growth. Body mass analysis was conducted by dual X-ray absorptiometry (DXA) on the 6^{th}, 8^{th}, and 10^{th} weeks of the trial. HF animals gained more weight after 7 weeks, had greater body fat than the LF animals, and similar glucose responses to the oral glucose challenges. HF rats secreted more insulin and leptin compared to LF animals. Lean body mass and GH concentrations were not different between the groups. Results of this study demonstrate that leptin but not GH is involved in the development of insulin resistance in growing rats as a result of excess energy intake in the form of dietary fat.

Introduction

Overweight and obesity are growing health concerns in industrialized nations such as the USA, where caloric intake is increasing and physical activity is decreasing, especially among the young (1). Excess body weight and body fatness contributes to health conditions such as heart disease, dyslipidemias, and type 2 diabetes mellitus (2). Obese individuals produce twice the amount of leptin compared to slender individuals, and there is evidence indicating this is due to increased production of leptin by subcutaneous adipocytes compared to visceral fat cells (3;4). (5-9)

Body fat is positively correlated with leptin concentration, which is positively correlated to insulin resistance and negatively correlated with insulin-stimulated glucose uptake (10).(11) Frequently, type 2 diabetes, which is characterized by insulin resistance and impaired glucose tolerance, is not diagnosed until overt symptoms such as weight loss, increased appetite, and frequent urination develop (12).

Diets high in fat are known to increase body weight and fat mass, induce alterations in carbohydrate and lipid metabolism, lead to insulin resistance, and increase production and release of leptin in humans, rodents, and other animals (5;13-16). High-fat diets providing excess energy contribute to increased body weight and body fat accumulation, impaired glucose tolerance and insulin resistance in laboratory animals and humans, but the mechanism by which this occurs is not clear (17).

During puberty, growth hormone (GH) is associated with increased glucose-stimulated insulin secretion (18), and is inversely related to pubertal insulin sensitivity (19). GH secretion is pulsatile in nature, with fluctuations occurring in rats every 2 to 4

hours (20). This study was designed to examine the effects of HF diets in promoting impaired insulin sensitivity in female rats during rapid growth and sexual maturation.

Materials and Methods

Twenty female weanling Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) were randomly assigned to one of two diets (Table 1). Animals were 21 days of age on arrival, and were housed individually in suspended wire bar-floor cages. Body weight (BW) in grams was recorded on arrival, and weekly thereafter. Animals were fed their assigned diets on the day of arrival and for the duration of the study. All animals had free access to water and were kept on a 12:12 light: dark cycle (lights on at 0700).

Diet composition and energy value are outlined in Table 1. Diet treatments were a 10% fat by weight diet (LF) and a 20% fat by weight diet (HF). Both diets were prepared to provide equal vitamins and minerals per calorie, and contained equal percentages by weight of protein and fiber. Based on a projected weight of 100 g at 5 weeks of age, the maximum expected energy requirement (21) during the first 2 weeks of feeding trial was approximately 40 kcal/ day. Based on a projected BW of 250 g by the end of the study, maximum daily energy requirements for the animals was calculated to be 53 kcal/ day. Animals were intentionally provided calories in excess of energy requirement for this study. For the first 2 weeks, animals received 53 kcal per day. After 2 weeks of diet treatment, diet was increased to provide 65 kcal per day. Food intake was measured 24 h preceding each DXA measurement for 3 or 4 animals in each treatment group.

After 5, 7, and 9 weeks of treatment diets, oral glucose tolerance tests (OGTT)

were administered to animals following an overnight fast. Free access to deionized drinking water was allowed during the fast. On the morning of the OGTT, animals were weighed, then approximately 1.0 mL of fasting blood was collected via the tail vein. Blood glucose was determined using a DEX glucometer (Bayer Corporation, Elkhart, IN). Each animal then received 2 g glucose/ BW_{kg} by gavage. Blood samples were taken from the tail vein at 30, 60, and 120 min after the glucose administration. The first drop of blood at each collection time was used to determine blood glucose concentration using the DEX. The glucometer was calibrated on each day of glucose tolerance testing, and all calibrations were within the acceptable range. The inter-assay coefficient of variation for glucose was 5%.

At 6, 8, and 10 weeks of diet treatment (when rats were 9, 11, and 13 weeks of age), animals were sedated with 58 mg/ BW_{kg} ketamine HCl and 2.9 mg/BW_{kg} xylazine for body composition analysis. A model 4500 Elite Dual X-ray Absorptiometry machine (DXA, Hologic, Waltham MA) was then used to determine body fat mass, percentage of body fat, and lean body mass. Animals were necropsied following the last DXA, after 10 weeks of diet treatment.

Serum insulin, leptin, and growth hormone (GH) were determined by radioimunoassay (RIA, Linco Research, Inc., St. Charles, MO). Intra- and inter-assay coeffecient of variation (CV) were 10.3% and 7.8% for insulin, 7.1% and 7.4% for leptin, respectively. GH was analyzed in a subset (n = 16) of the animals studied. Intra-assay CV for GH was 7.0%.

SAS Version 8 Statistical Analysis Software for Windows was used to analyze all data. The Mixed procedure was used to determine significant main effects and their

interactions, with the Slice procedure used to determine differences between groups. Pearson correlation coefficients were determined using the Corr procedure. The level of significance (α) was set at $p \leq 0.05$.

Results

Body weights of rats in both groups were not different until after the seventh week of diet treatment. After the seventh week of diet treatment, HF animals weighed significantly more than LF animals ($P < .05$, Fig. 1). HF rats had significantly higher body fat percent (fig. 2), as well as body fat mass than LF rats. Lean body mass was not different between groups throughout the experiment (fig. 3). Food energy intake was not different between groups. Table 2 shows a comparison between groups for body fat percent, body fat mass, lean body mass, and food intake over time.

No significant differences in blood glucose levels between groups at fasting or in response to the oral glucose challenges were observed at all time points. Area under the curve (AUC) for blood glucose response was not different between groups. In the HF group, blood glucose concentrations peaked at 60 min after each glucose challenge, while glucose concentrations seemed to plateau between thirty and sixty minutes post-challenge in the LF group. Rats in both groups exhibited a failure of blood glucose to return to fasting levels two hours after the glucose load (fig. 4).

Fasting serum insulin concentrations at both the OGTT 2 and OGTT 3were higher ($p < .05$) in the HF group than in the LF group. Insulin levels were significantly higher ($p < .05$) in the HF group at 30 min during OGTT 1 and at 120 min during OGTT 2. During the OGTT 1, peak insulin response in LF rats was at 60 min compared to HF, although

this delay in insulin response did not persist to subsequent OGTTs. The insulin response AUC for the OGTT 1 and OGTT 2 were significantly greater ($p < .05$) for HF rats than LF rats, with a tendency for significance ($p < .1$) at OGTT 3 (fig. 5).

Mean serum leptin concentrations in response to OGTT 1 were significantly greater ($p < .05$) at 30 min and 2 h after the glucose load was administered. Serum leptin concentrations at OGTT 2 were higher in the HF animals 2 h after the glucose challenge ($p < .0001$). At OGTT 3, serum leptin levels of the HF rats were significantly greater ($p < .001$) at 1 h and 2 h after glucose administration. The serum leptin AUC was greater in HF rats at OGTT 1 and OGTT3 ($p < .05$ and $p < .001$, respectively). Leptin AUC was not significantly different between groups during OGTT 2 (fig. 6). No differences were found between groups in serum growth hormone responses at any time point of any glucose tolerance test (data not shown).

Significant positive correlations were observed between body weight and fasting insulin at all OGTTs (range: $p < .02$ to $p < .0006$) and with fasting leptin concentrations at OGTT 1 ($p < .05$) and OGTT 3 ($p < .05$). Percent body fat throughout the study was positively correlated (range: $p < .02$ to $p < .0001$) with fasting insulin and with fasting leptin concentrations at OGTT 1 with DXA 1 ($p < .002$), OGTT 3 to DXA 2 ($p < .05$) and OGTT 3 to DXA 3 ($p < .01$). Fasting leptin and insulin concentrations were positively correlated at OGTT 1 ($p < .0009$) and OGTT 3 ($p < .004$). Body weight was significantly correlated with percent body fat at DXA 2 and DXA 3. All significant correlations in this discussion are found in Table 3 (complete correlation tables are in Appendix D).

Discussion

This study was undertaken to determine the relationships between body composition and certain hormones in the development of diet induced insulin resistance. The HF diet was designed to resemble the total fat content of the typical American diet (1).

The increased body weight of HF rats over LF rats is not explained by energy consumption, as the total cumulative difference in energy intake between groups, based on mean intake for each group, is calculated to be 22.4 calories, approximately the equivalent of two grams of body fat. Researchers have described HF rats which gain a disproportionately greater amount of body weight than would be expected based on energy intake (13;22). This increased energy efficiency may be due to a lack of increased heat production post-feeding in the HF rats, as was seen in a study conducted by Storlien and colleagues (6). Others have suggested that storage of ingested fat requires less energy than conversion of consumed carbohydrate into fat stores (23). Such differences in macronutrient partitioning may account for the increased body weight without evidence of increased energy consumption.

Our finding that HF rats consumed equivalent amounts of energy to LF rats is consistent with the finding that HF rats' caloric intake is not increased over that of controls (24). However, others have described increased initial energy consumption in SD rats fed HF diets compared to LF fed animals, which accounted for increased body weight that was evident early and persisted beyond the point that energy consumption equalized between groups (25). The difference in body weight between groups in this study was not evident before the seventh week of diet treatment, therefore, it is doubtful

that initially increased energy intake in HF rats is the cause of the body weight disparity between groups.

HF rats in this study accumulated significantly greater fat mass than LF animals before significant increases in body weight were detected. Findings such as these were evident in male rats fed HF diets from 6 to 18 weeks of age (26). The increased body fat in HF animals, coupled with no difference in lean body mass between groups, indicates that HF diets indeed cause increased body fat accretion in comparison with consumption of equivalent energy from primarily carbohydrate. If HF animals simply grew larger than LF animals in this study, we could not draw the same conclusion.

That rats receiving both treatments displayed a failure to return to fasting blood glucose (BG) concentrations by 2 h post-load following the 2 g/ BW_{kg} oral glucose challenge is interesting. Others (27) reported that in adult male Wistar rats consuming either 11% or 45% of calories from fat, the HF animals displayed a failure to return to fasting BG within 2 h. It may be that 22% of calories from fat is greater than is easily tolerated by this strain of rat, or that in female rats, the insulin resistance during puberty, observed in humans (28), lasts beyond 13 weeks of age. Another possible explanation for the sustained elevation in BG concentrations is that rats were fasted overnight before the OGTTs. Because the room the animals were housed in was not on a reverse light-dark cycle, the rats were fasted during their active cycle.

Mid-pubertal insulin resistance may also account for the increased insulin secretion at all time points of the second OGTT over the first and third OGTTs for both the HF and LF groups. A post-adolescent recovery of insulin sensitivity could also account for the overall decrease in insulin secretion at the third OGTT to levels similar to

those seen at the first OGTT, when animals were 56 days old, the onset of sexual maturity in rats.

Researchers have shown that leptin responds to energy intake by initially declining slightly, if at all, then increasing steadily between the first postprandial hour and several hours postprandially (29;30). With the exception of the HF group at the first OGTT, this same pattern is evident in both treatment groups at each OGTT. It is notable, however, that leptin concentrations significantly increased over fasting in HF but not LF rats at each OGTT, evidenced by the significant difference between groups in leptin concentrations at each 2-h post-load time point. The lack of leptin rise in a lean versus an obese subject was also noticed by Chapelot and colleagues (29). This may be attributed to hypersecretion of insulin by HF rats, as leptin has been shown to be released in response to insulin both in vitro and in vivo (31). Levy and colleagues (32) observed that in male SD rats, increases in serum leptin concentrations were not different between HF and LF rat groups following an intravenous infusion of glucose or an 8 g chow meal at three hours after administration. The difference between our findings and these may be due to age, body composition, and gender differences between animals in each study.

Observed mean GH levels in this study are consistent with the literature. Tannenbaum, et al. sampled GH every 15 min over 6 h, and found no difference between HF and LF rats (9). Similarities between the HF and LF rats may be due to the relatively small number of samples (n = 5 to 14 samples per time point) available for GH analysis. Alternatively, because GH is secreted in pulses (20), a more frequent sampling schedule may be needed to discern differences in temporal GH secretory patterns. In GH concentrations may have been similar between groups because diet had no effect on GH.

Another possibility is that animals in both groups were experiencing similar lean body mass accretion. This also demonstrates the inability of GH to promote lipolysis and suppress fat accretion.

A lack of difference in mean GH levels indicates that the increased insulin resistance in the HF group cannot be ascribed to differences in GH secretion. Instead, the present data indicates that increased leptin secretion may precipitate increased insulin resistance. In support of the latter suggestion, we observed significant positive correlations between plasma insulin and leptin concentrations. The precise mechanism by which leptin induces insulin resistance remains to be elucidated.

In conclusion, rats fed HF diets had significantly greater body mass, body fat mass and percent body fat, and these changes were associated with increased serum leptin concentrations. Lean body mass was not different between groups, nor were blood glucose or serum GH concentrations. High-fat diet significantly increased serum insulin and leptin concentrations in response to oral glucose tolerance tests. Results of this study demonstrate that leptin but not GH is involved in the development of insulin resistance in growing rats as a result of excess energy intake from dietary fat.

Table 1. Composition and energy value of experimental diets.

	Low-fat diet		High-fat diet
		g/kg Diet	
Casein	200		200
Cornstarch	100		100
Sucrose	500		400
Cellulose	50		50
Soybean oil	100		200
Mineral mix*	35		39.3
Vitamin mix†	10		11.2
L-Cysteine	3		3
Choline Bitartrate	2		2
		% kcal	
CHO	58		43
Fat	22		39
Protein	20		17
		kcal/ g diet	
Energy Density	4.10		4.57

* Mineral mix composition, g/ kg mix: $CaCO_3$, 357; KH_2PO_4, 196; $K_3C_6H_5O_7$•H2O, 70.78; NaCl, 74; K_2SO_4, 46.6; MgO, 24: $FeCl_2$•$6H_2O$, 3.6; $ZnCO_3$, 1.65; $MnCO_3$, 0.63; $CuCO_3$, 0.3; KIO_3, 0.01; Na_2SeO_4, 0.01; NH4MoO4•H20, 0.008; Na_2SiO_2, 1.45; $LiCl_2$, 0.017; H_3B0_3, 0.08; NaF, 0.064; $NiCO_3$, 0.032; NH_4VO_3, .0066.

† Vitamin mix was obtained from Teklad, Madison, WI, catalog #40060.

Table 2. Body mass analyses and food intake of rats fed high-fat and low-fat diets at 6, 8, and 10 weeks of diet treatment. Values given are mean ± SEM for body composition data, mean ± SD for food intake.

	HF	*6 weeks*	*LF*
Rats per group	n=10		n=10
% Body Fat	13.2 ± 0.7		9.3 ± 0.7*
Body Fat, g	25.6 ± 1.5		17.1± 1.5*
Lean Body Mass, g	161.5 ± 3.1		162.2 ± 3.1
Food Intake, kcal/ day	57.0 ± 1.5		56.5 ± 4.6
		8 weeks	
Rats per group	n=9		n=10
% Body Fat	13.0 ± 0.5		9.0 ± 0.5†
Body Fat, g	28.3 ± 1.3		18.9 ± 1.3†
Lean Body Mass, g	183.5 ± 3.5		183.0 ± 3.5
Food Intake, kcal/ day	52.2 ± 2.0		57.3 ± 2.8
		10 weeks	
Rats per group	n=8		n=8
% Body Fat	13.1 ± 0.5		8.7 ± 0.5†
Body Fat, g	30.1 ± 1.4		19.0 ± 1.5†
Lean Body Mass, g	192.2 ± 3.8		193.6 ± 4.0
Food Intake, kcal/ day	56.5 ± 8.0		51.6 ± 3.3

*P < .0005, †P < .0001 for significance between groups.

Table 3. Pearson correlation coefficients among fasting blood parameters, body weight, and body fat percent in rats fed low-fat or high-fat diets.

	Body Weight	DXA #1 Body Fat %	DXA #2 Body Fat %	DXA #3 Body Fat %	Fasting Leptin
OGTT #1					
Insulin	0.59*	0.60†	--	--	0.75†
Leptin	0.51*	0.71†	--	--	--
Body weight	--	0.35	--	--	0.51*
OGTT #2					
Insulin	0.55*	0.59*	0.57*	--	0.33
Leptin	-0.02	0.18	0.24	--	--
Body weight	--	0.42‡	0.48*	--	-0.02
OGTT #3					
Insulin	0.76†	--	0.74†	0.86†	0.68†
Leptin	0.53*	--	0.50*	0.61*	--
Body weight	--	--	0.46*	0.53*	0.53*

*$p < .05$, †$p < .001$ for significance of relationship between variables, ‡Tendency for significance, $p < .10$. ($n = 15$ to 20)

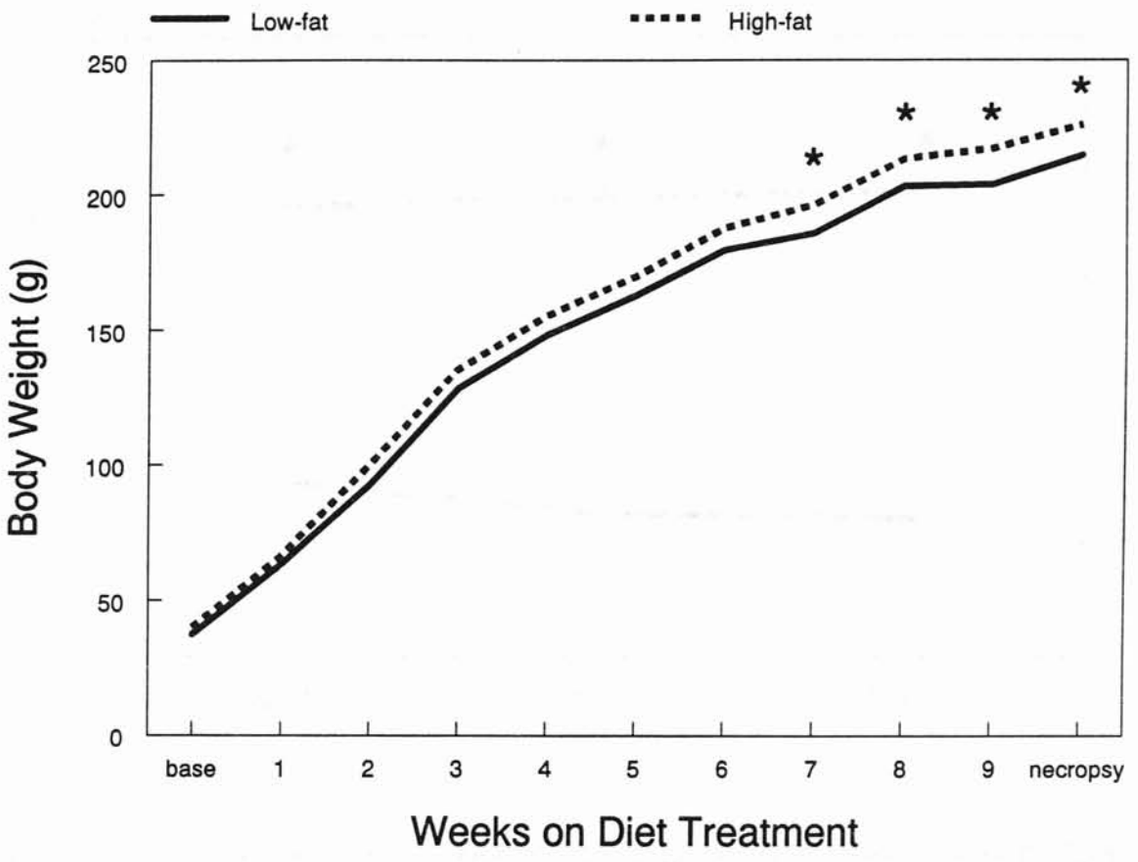

Figure 1. Baseline and weekly body weights of female rats fed low-fat (LF) or high-fat (HF) diets. *P < .05 significant difference of body weight between groups; n = 9 to 10 rats per group.

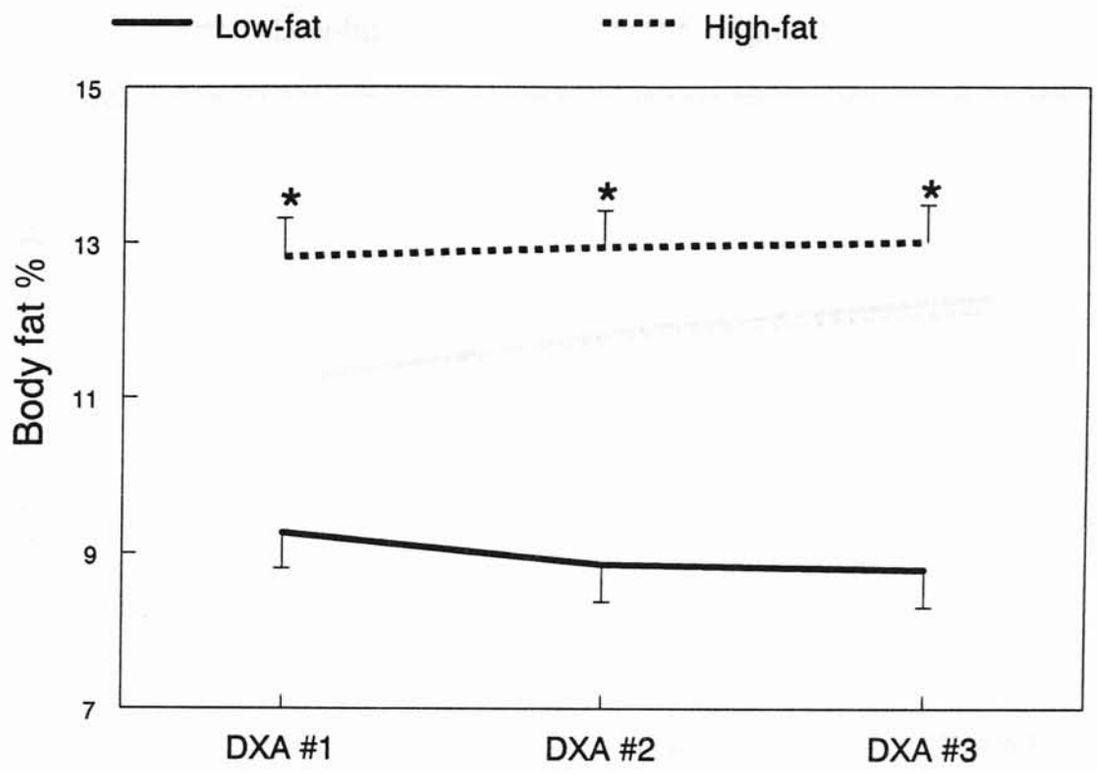

Figure 2. Percentage of body fat in female rats fed low-fat (LF) or high-fat (HF) diets after 6, 8, and 10 weeks of diet treatment, as measured by Dual X-ray Absorptiometry (DXA) analysis. *$p < .0001$ for difference between LF and HF groups; n=8 to 10 rats per group.

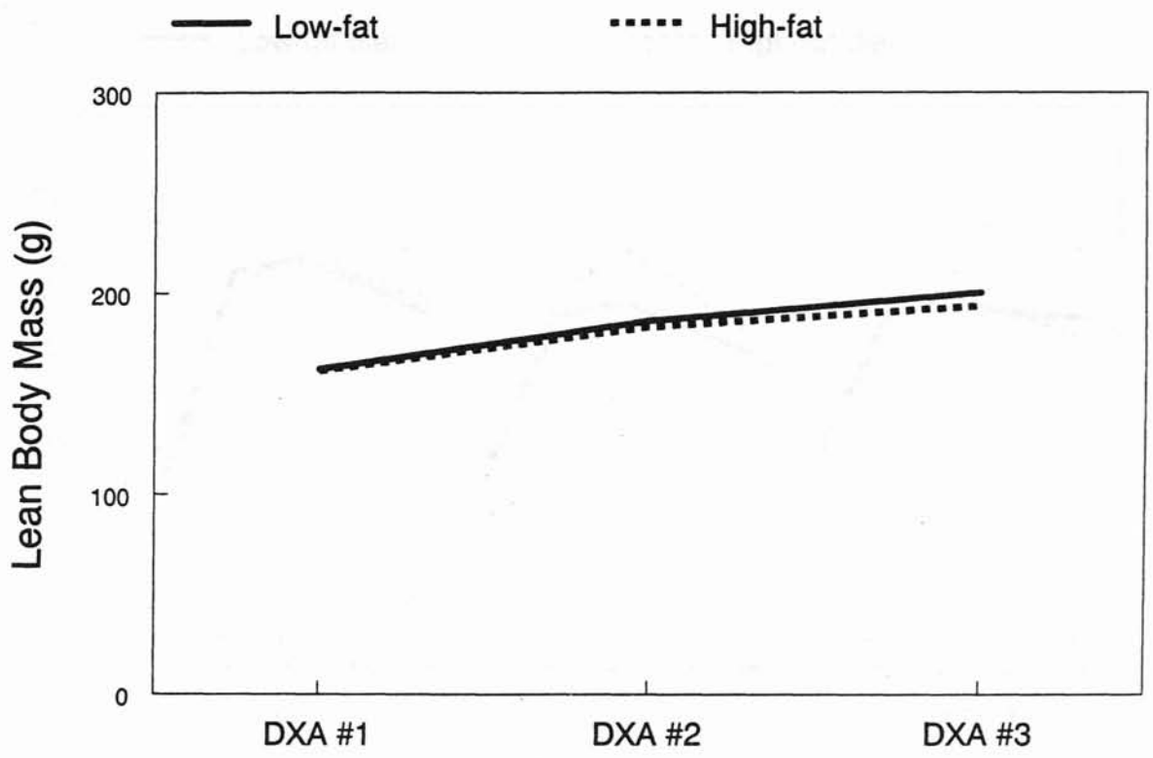

Figure 3. Lean body mass of female rats fed low-fat (LF) or high-fat (HF) diets after 6, 8, and 10 weeks of diet treatment, as determined by Dual X-ray Absorptiometry (DXA) analysis; n = 9 to 10 rats per group.

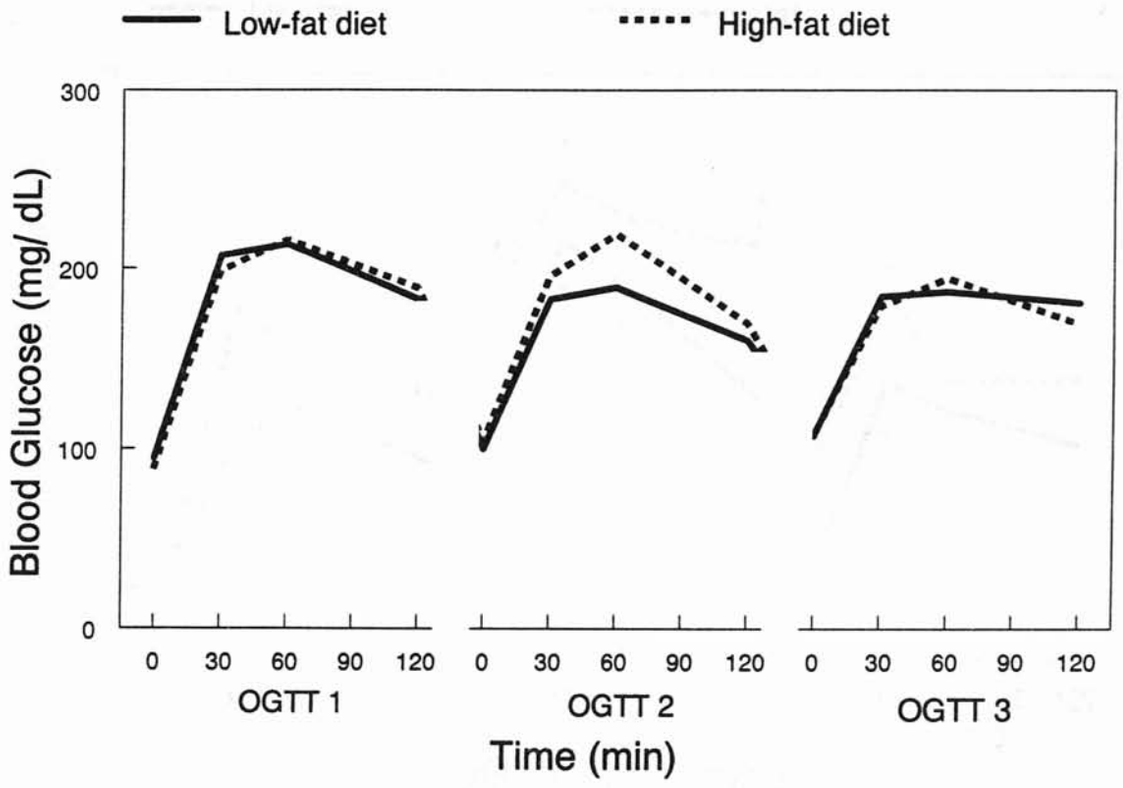

Figure 4. Blood glucose concentrations of rats fed low-fat or high-fat diets at fasting (0 min) and in response to a 2 g/ BW_{kg} oral glucose challenge following 5, 7, and 9 weeks of diet treatment; n = 8 to 10 rats per group per time point.

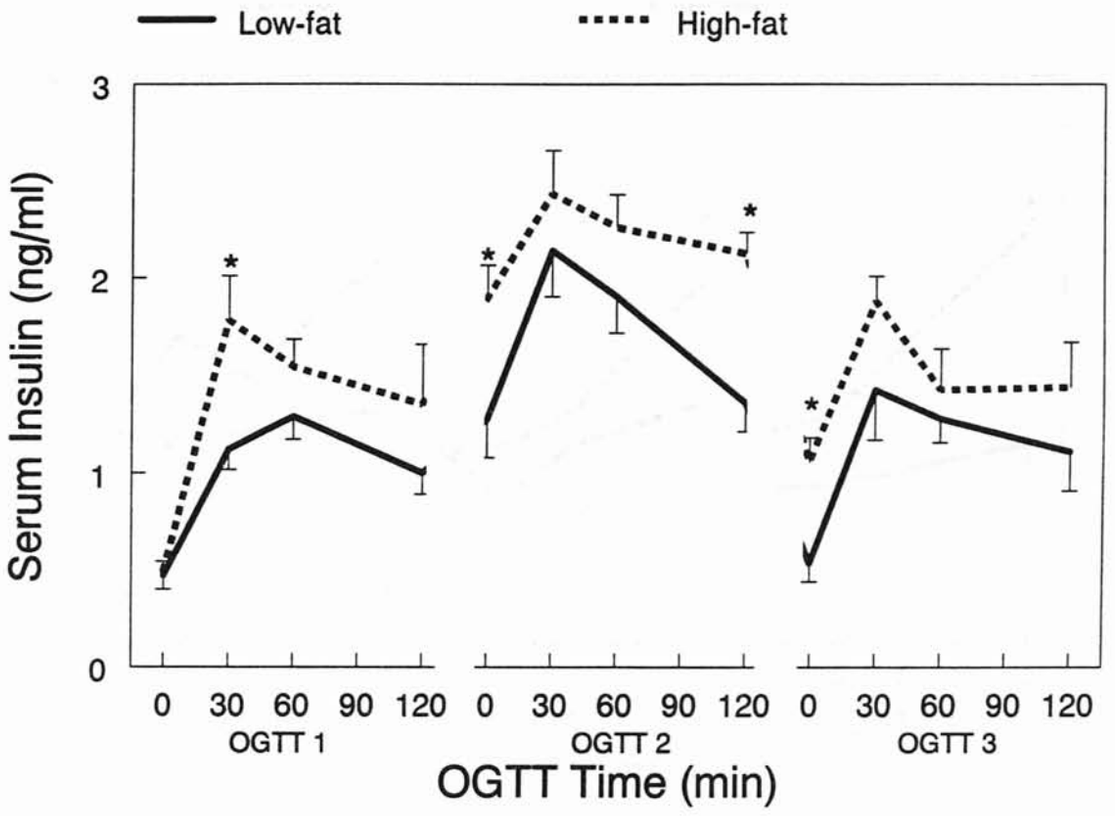

Figure 5. Serum insulin concentrations of rats fed low-fat (LF) or high-fat (HF) diets at fasting (0 min) and in response to a 2 g/ BW_{kg} oral glucose challenge following 5, 7, and 9 weeks of diet treatment; n = 8 to 10 rats per group per time point.

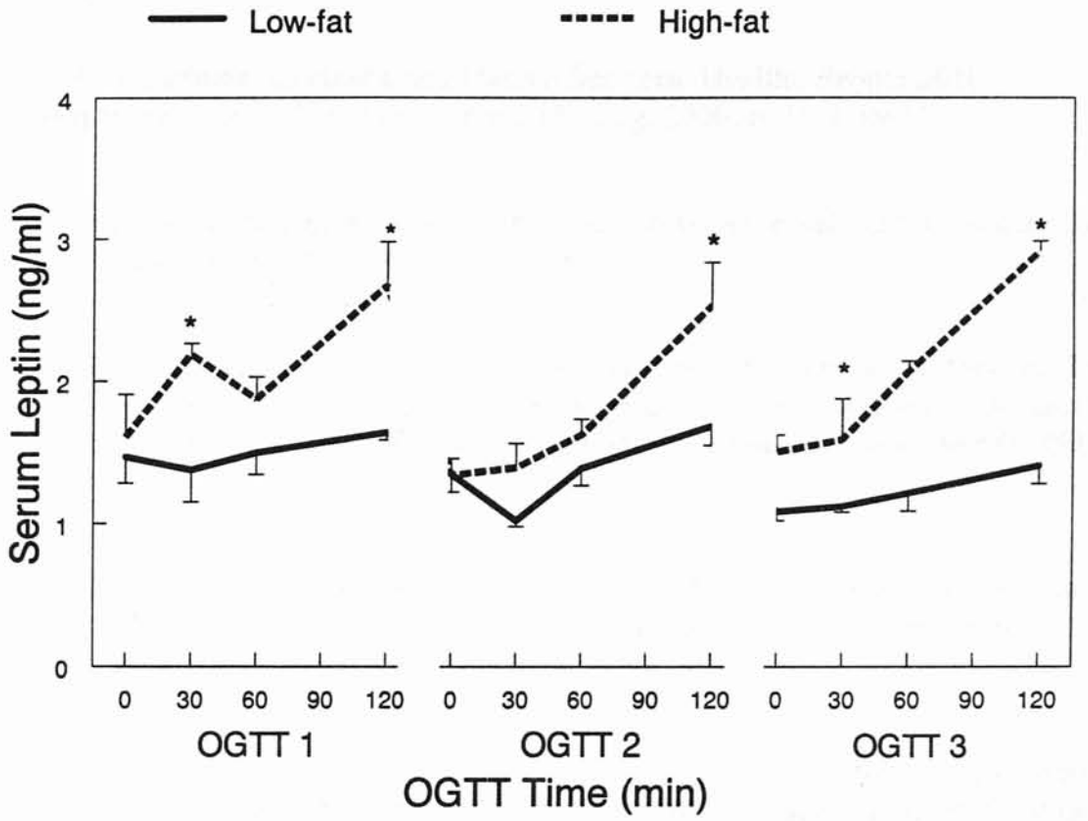

Figure 6. Serum leptin concentrations of rats fed low-fat (LF) or high-fat diets (HF) at fasting (0 min) and in response to a 2 g/ BW_{kg} oral glucose challenge following 5, 7, and 9 weeks of diet treatment; n = 8 to 10 rats per group per time point.

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CHAPTER V

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

Summary

This study was designed to examine the effects of HF diet on body composition and leptin, insulin, and GH responses to OGTTs. Twenty female weanling SD rats were randomly assigned to receive either a HF (39% kcals from fat) or LF (22% kcals from fat) diet upon arrival. Animals were provided excess food energy in comparison to their calculated requirements, and animals in each group were given the same number of kcal daily (53 ± 0.5 kcal the first 2 weeks, 65 ± 0.5 kcal for the remainder of the study). Oral glucose tolerance tests were performed after 5, 7, and 9 weeks of diet treatment. Animals received a 50% glucose solution (2 g/ BW_{kg}) via gavage glucose following an overnight fast. Blood was sampled at fasting and at 30, 60, and 120 min after the glucose load for measurement of BG and serum insulin, leptin, and GH. Body mass analysis was conducted by DXA under ketamine/ xylazine sedation after 6, 8, and 10 weeks of diet treatment.

HF diet induced greater body weight gain and body fat accretion, which were observed after 6 weeks of diet treatment. Insulin resistance was evidenced by significantly greater insulin AUCs in the HF rats compared to the LF rats at OGTT 1 and OGTT 2, as well as increased fasting insulin concentrations at OGTT 2. Leptin secretion

was greater in HF rats during all OGTTs compared to the LF rats, although fasting levels of leptin were not different between groups. GH concentrations were not different between groups at any time point, which indicates that diet did not influence GH secretion, and that rats in both groups had similar GH secretion.

Conclusions

In order to test the following hypotheses, the objectives of this study were to determine the effects of dietary fat content on growth (weight gain) and adiposity (% body fat) in rats isocalorically fed diets that have high or low fat content and to determine the effects of dietary fat content on glucose, insulin, leptin and growth hormone responses to oral glucose tolerance tests over time. Each hypothesis is addressed below.

H_1 Rats fed HF diets will have greater total body mass and body fat content compared to rats isocalorically fed LF diets.

In this study, rats fed HF diets developed greater body mass ($p < .05$) compared to LF rats, which was evident after 7 weeks of diet treatment. Body fat content, expressed as a percentage of body mass, was greater in HF rats than LF rats after 6 weeks of diet treatment ($p < .005$).

H_2 Rats fed HF diets will produce significantly higher leptin responses to oral glucose tolerance challenges compared to rats isocalorically fed LF diets during growth.

Although fasting leptin concentrations were not significantly different between groups, HF rats had significantly greater serum leptin concentrations 2 h after oral glucose administration ($p < .0001$) compared to fasting while LF rats did not exhibit significant increases in leptin concentrations compared to fasting. 2-hour leptin

concentrations were significantly greater in HF rats compared to LF rats at all OGTTs ($p < .05$ to $p < .0001$).

H_3 Rats fed high-fat diets will develop insulin resistance, evidenced by amplified insulin responses to oral glucose tolerance tests, compared to isocalorically low-fat fed rats.

In maintaining similar BG concentrations at all OGTTs, HF rats had greater insulin concentrations at fasting during OGTT 2 and 3 ($p < .05$), and in response to OGTT 1 and 2 ($p < .05$). This demonstrated that HF rats required more endogenous insulin to promote glucose uptake by the tissues.

H_4 GH concentrations of rats fed high-fat diets will not be different from growth hormone concentrations of rats isocalorically fed low-fat diets.

GH concentrations were not different between HF and LF rats at any point during the OGTTs.

As a result of this study, it is hypothesized that HF diets induce insulin resistance through the effects of leptin's action on or involvement in a variety of pathways, such as:

- Inducing insulin resistance at the peripheral tissues through its effect on insulin receptors or post-receptor antagonism of the insulin signaling pathway,
- In obesity, the ratio of freely circulating leptin to that bound to carrier proteins in the blood is altered,
- Its relationship to the production of proteins such as protein tyrosine-phosphatase 1B (PTP-1B), ghrelin, or resistin, which are newly discovered molecules involved in insulin resistance or satiety,
- Its relationship to cytokine production or other hormones such as glucocorticoids.

Recommendations

This study was designed to evaluate the effects of high-fat feeding during rapid growth in female rats. Due to limited resources, we were not able to examine rats younger than 56 days of age. Ideally, a larger, longitudinal study using more rats, and rats of both genders, would allow examination of the effects of chronic HF diet on body composition and hormonal changes resulting from diet treatment both earlier and later in treatment duration. A study such as this may also offer insight into whether the body composition and hormonal variations we have seen occur in both genders at the same age. It would also provide an opportunity to examine the effects of life-long HF diet consumption and resultant body composition alterations on all of the parameters examined herein. Such a study conducted in another rat species, such as Fisher 344 or Wistar rats, may provide further insight into the development of diet-induced obesity and/ or diabetes.

In this study, although equal amounts of vitamins and minerals were provided per kcal, protein and fiber content were not adjusted per kcal. This difference in treatments may have had some unknown effect on the outcome of the study, but the difference in protein and fiber per kcal were very small. To exclude the possibility of these differences affecting study outcomes, future research diets should be adjusted to provide equal amounts of dietary components per kcal, so that fat is the only dietary variable.

Leptin serves as a feedback inhibitor on insulin secretion in both humans and rodents. One other limitation of this animal study is that rodents do not develop leptin resistance as observed in humans. Research into the cellular mechanism of leptin resistance in humans is called for to elucidate the exact role leptin plays in dietary fat-

induced insulin resistance. Possible methods for examining the cellular mechanism of leptin at the cellular level include microarray and RT PCR studies on both muscle and adipose tissue of animals to determine leptin's relationship to gene expression of potential molecules involved in cellular insulin resistance.

Longitudinal studies should be conducted to determine if type 2 DM can be induced by chronic HF feeding. As has been observed in humans, type 2 DM develops from insulin resistance when preventive interventions are not implemented.

Well-controlled dietary studies in humans are few and difficult to conduct. Ideally, a well-controlled feeding study in human subjects for an extended period of time would be in order to examine the changes in body composition and the plethora of hormones related to insulin sensitivity and the body's ability to maintain normal glucose homeostasis.

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APPENDICES

APPENDIX A

Studies examining the effects of high-fat diets in rodents.

Author, year	HF diet % fat/ source	Strain/ gender/ weight or age	N	Duration of diet treatment	Method of evaluation/ glucose dose
Wilkes, 1998	60% kcal/ safflower oil	SD/ male/ 200g	45	3 weeks	Intravenous glucose tolerance test (IVGTT)/ 300 mg.BW_{kg}
Pawlak, 2001	60% kcal/ ?	Albino Wistar/ ?/ 215 g	?	4 weeks	IVGTT/ 1 g/ BW_{kg}, hyperinsulinemic euglycemic clamp
Commerford, 2000	45% weight/ ?	Crl(WI)BR/ male/ 7 weeks	92	5 weeks	Fasting blood parameters
Fryer, 1993	55% kcal/ lard	Ludwig Wistar/ ?/ 80-100 g	24	6 weeks	OGTT/ 400 mg/ BW_{kg}
Buettner, 2000	45% kcal/ safflower oil	Wistar/ male/ 150-175 g	8	6 weeks	OGTT/ 2 g/BW_g
Kim, 2000	50% kcal/ lard & corn oil	Wistar/ male/ weanling	60	4 weeks	Muscle incubation, 2-DG uptake
Steinberg, 2000	60% kcal/ safflower oil	SD/ female/ 165 g	?	4 weeks	Muscle pulse-chase clamp study
Storlien, 1991	59% kcal/ varying sources	Wistar/ male/ 280 g, 54 days	?	30 days	Hyperinsulinemic euglycemic clamp
Ahren, 1997	58% kcal/ ?	C57BL/6J (mice)/ female/ 4 weeks	?	1, 2, 6, 10 months	Non-fasting blood parameters
Wang, 1998	Choice diet paradigm/ ?	SD/ ?/ ?	?	4-5 weeks	Non-fasting blood parameters
Oakes, 1997	59% kcals/ ?	Wistar/ male/ 250 g	?	3 weeks	Hyperinsulinemic euglycemic clamp
Kraegen, 1991	59% kcals/ safflower oil	Wistar/ male/ 300-380 g	?	3 days & 3 weeks	IVGTT, 500 mg/ BW_{kg} / Hyperinsulinemic euglycemic clamp
Levy, 2000	24% weight/ ?	SD& Fischer 344/ male/ 2 months	?	6 weeks	IV Glucose infusion, 6.8 g/ BW_{kg}
Storlien, 1986	59% kcal/ safflower oil	Wistar/ male/ 300g	29	3 days & 3 weeks	Mid-physiologic euglycemic clamp
Tannenbaum, 1997	20% weight/ corn oil	Long-Evans/ male/ Adult	20^A 17^B	5 days, 1 week, 3 weeks, 9 weeks, 12 weeks	[A] non-fasting blood parameters [B] Insulin tolerance test, 0.125 mU/BW_{kg}
York, 2001	56% kcal/ ?	Osborn-Mendel/ male/ 12 weeks	50	80 days	Non-fasting blood parameters

Author, year	HF diet % fat/ source	Strain/ gender/ weight or age	N	Duration of diet treatment	Method of evaluation/ glucose dose
Kim, 2000	66.5% kcal/ shortening & corn oil	SD/ male/ ?	36	3 weeks	Hyperinsulinemic euglycemic clamp
Mooradian, 2000	90.7% kcal/ ?	Fischer 344/ ?/ 3 month	50	10 days	Non-fasting blood parameters
Ahren, 1998	58% kcal/ ?	C57BL/6J mice/ female/ 4 weeks	68[A] 163[B]	1.5 years	[A] Intraperitoneal glucose tolerance test [B] Non-fasting blood parameters
Ainslie, 2000	36% kcals/ ?	Hooded Wistar/ female/ 20-22 weeks	70	4 weeks	Non-fasting blood parameters

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APPENDIX B

OKLAHOMA STATE UNIVERSITY

OSU

Institutional Animal Care and Use Committee
Stillwater, Oklahoma 74078
405-744-7631

September 18, 2000

Institutional Animal Care and Use Committee Action

This protocol was reviewed by the IACUC with the following action:

Principle Investigator: Dr. Maria Spicer

Department: Nutritional Sciences

Protocol Title: Effects of Chromium and sucrsose feeding on metabolic hormones and subsrate utilization

Protocol Number: HE-01-16

Animal Number and Species: 80 Rats

Expiration Date: 9-30-03

Approval ___XX___ Deferral _____

Approval with Modifications _____

Comments:

Date of final Institutional Committee Action 9-7-00

Signature of IACUC Chairman Katherine M. Keen Date 9/19/00

Signature of IACUC Veterinarian Karen Vargas Date 9/18/00

Institutional Assurance Number A3722-01

For Committee Administrative Purposes Only

____ Additional information was requested and has been provided by P.I.

____ Significant modifications to ACUF were requested (see attached information).

Bringing Dreams to Life

APPENDIX C

COMPOSITION OF MINERAL MIX, g/ kg:

Calcium carbonate, anhydrous, 40.04% Ca	357
Potassium phosphate, monobasic, 22.76%P, 28.73% K	196
Potassium citrate, tri-potassium, monohydrate, 36.16% K	70.78
Sodium chloride, 39.34% Na, 60.66% Cl	74
Potassium sulfate, 44.87% K, 18.39% S	46.60
Magnesium oxide, 60.32% Mg	24
Iron(II) chloride, 28.1% Fe	3.60
Zinc carbonate, 52.14% Zn	1.65
Manganous carbonate, 47.79% Mn	0.63
Cupric carbonate, 57.47%Cu	0.30
Potassium iodate, 59.3% I	0.01
Sodium selenate, 41.79% Se	1.0
Ammonium paramolybdate, 4 hydrate, 54.34% Mo	1.0
Sodium metasilicate, anhydrous	0.6228
Lithium chloride, 16.38% Li	0.017
Boric acid, 17.5%B	0.082
Sodium fluoride, 45.24% F	0.064
Nickel carbonate, 45% Ni	0.032
Ammonium 43.55% V	0.0066

APPENDIX D

Correlations Among Variables
OGTT 1 to DXA 1

The CORR Procedure

20 Variables: ratid trmt lep0 lep30 lep60 lep120 weight gluc0 gluc30 gluc60 gluc120 ins0 ins30 ins60 ins120 bmcg fatg leang totg pctfat

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
ratid	20	15.00000	8.85557	300.00000	1.00000	29.00000
trmt	20	1.50000	0.51299	30.00000	1.00000	2.00000
lep0	16	1.81652	1.00892	29.06427	0.83401	5.03060
lep30	12	1.90897	0.63564	22.90767	0.66745	3.00810
lep60	13	1.64105	0.41723	21.33370	0.79100	2.33250
lep120	16	2.15923	0.80348	34.54760	1.38430	4.12200
weight	20	165.25800	11.07731	3305	137.41000	185.47000
gluc0	19	95.84211	15.69240	1821	62.00000	137.00000
gluc30	20	202.95000	25.09660	4059	154.00000	239.00000
gluc60	19	214.89474	31.30476	4083	169.00000	269.00000
gluc120	20	190.80000	45.74368	3816	134.00000	282.00000
ins0	20	0.55117	0.39028	11.02333	0.10000	2.00170
ins30	20	1.50125	0.63779	30.02490	0.61818	3.11200
ins60	19	1.49938	0.52225	28.48820	0.97515	2.94850
ins120	17	1.16808	0.39954	19.85731	0.47158	1.95910
bmcg	20	5.23500	0.42212	104.70000	4.20000	6.00000
fatg	20	21.33000	6.39392	426.60000	12.60000	41.10000
leang	20	161.84500	9.48359	3237	142.30000	175.70000
totg	20	188.41000	12.03621	3768	160.90000	209.50000
pctfat	20	11.24000	2.89689	224.80000	6.70000	19.70000

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ratid	1.00000	0.05793	0.23885	-0.06448	-0.07229	0.15485	0.13048
		0.8083	0.3730	0.8422	0.8145	0.5669	0.5835
	20	20	16	12	13	16	20
trmt	0.05793	1.00000	0.40077	0.68722	0.38946	0.66514	0.34992
	0.8083		0.1240	0.0135	0.1884	0.0049	0.1304
	20	20	16	12	13	16	20
lep0	0.23885	0.40077	1.00000	0.75343	0.33281	0.74330	0.51321
	0.3730	0.1240		0.0074	0.2905	0.0023	0.0420
	16	16	16	11	12	14	16

Correlations Among Variables
OGTT 1 to DXA 1

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
lep30	-0.06448	0.68722	0.75343	1.00000	0.88790	0.78564	0.75461
	0.8422	0.0135	0.0074		0.0032	0.0025	0.0046
	12	12	11	12	8	12	12
lep60	-0.07229	0.38946	0.33281	0.88790	1.00000	0.73354	0.43680
	0.8145	0.1884	0.2905	0.0032		0.0066	0.1356
	13	13	12	8	13	12	13
lep120	0.15485	0.66514	0.74330	0.78564	0.73354	1.00000	0.44159
	0.5669	0.0049	0.0023	0.0025	0.0066		0.0868
	16	16	14	12	12	16	16
weight	0.13048	0.34992	0.51321	0.75461	0.43680	0.44159	1.00000
	0.5835	0.1304	0.0420	0.0046	0.1356	0.0868	
	20	20	16	12	13	16	20
gluc0	-0.40550	-0.10751	0.46220	0.33778	-0.17242	0.11029	0.03163
	0.0850	0.6613	0.0828	0.2829	0.5921	0.6956	0.8977
	19	19	15	12	12	15	19
gluc30	-0.06986	-0.16966	-0.32883	0.08744	0.55832	-0.16878	0.10932
	0.7698	0.4746	0.2137	0.7870	0.0474	0.5321	0.6464
	20	20	16	12	13	16	20
gluc60	0.08443	0.04479	-0.01529	0.68478	0.54269	0.08056	0.40802
	0.7311	0.8555	0.9569	0.0140	0.0553	0.7668	0.0829
	19	19	15	12	13	16	19
gluc120	0.09394	-0.04037	-0.21411	-0.03931	0.35885	0.06468	0.11052
	0.6936	0.8658	0.4259	0.9035	0.2285	0.8119	0.6428
	20	20	16	12	13	16	20
ins0	-0.17486	0.21874	0.74770	0.67041	0.44296	0.54181	0.58521
	0.4609	0.3542	0.0009	0.0170	0.1295	0.0302	0.0067
	20	20	16	12	13	16	20
ins30	0.12726	0.45720	0.48286	0.68978	0.46788	0.57678	0.47379
	0.5929	0.0427	0.0582	0.0131	0.1069	0.0193	0.0348
	20	20	16	12	13	16	20
ins60	0.45885	0.08892	0.39393	0.44352	0.30571	0.50287	0.29858
	0.0481	0.7174	0.1463	0.1487	0.3097	0.0471	0.2144
	19	19	15	12	13	16	19

Correlations Among Variables
OGTT 1 to DXA 1

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ins120	0.22369	0.45289	0.77775	0.54228	-0.00558	0.55486	0.53457
	0.3881	0.0679	0.0017	0.0848	0.9870	0.0395	0.0271
	17	17	13	11	11	14	17
bmcg	-0.26892	0.27951	0.38137	0.53657	0.25642	0.20644	0.77272
	0.2516	0.2327	0.1450	0.0721	0.3978	0.4430	<.0001
	20	20	16	12	13	16	20
fatg	-0.12865	0.68678	0.72599	0.75337	0.20773	0.68455	0.51530
	0.5888	0.0008	0.0015	0.0047	0.4959	0.0034	0.0201
	20	20	16	12	13	16	20
leang	-0.07796	-0.03624	-0.00487	0.38098	0.34164	-0.05020	0.80153
	0.7439	0.8794	0.9857	0.2218	0.2533	0.8535	<.0001
	20	20	16	12	13	16	20
totg	-0.13861	0.34608	0.38370	0.68766	0.35437	0.30367	0.93254
	0.5600	0.1350	0.1423	0.0135	0.2348	0.2529	<.0001
	20	20	16	12	13	16	20
pctfat	-0.11530	0.69770	0.71323	0.70377	0.11317	0.71160	0.34644
	0.6283	0.0006	0.0019	0.0106	0.7128	0.0020	0.1346
	20	20	16	12	13	16	20

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
ratid	-0.40550	-0.06986	0.08443	0.09394	-0.17486	0.12726	0.45885
	0.0850	0.7698	0.7311	0.6936	0.4609	0.5929	0.0481
	19	20	19	20	20	20	19
trmt	-0.10751	-0.16966	0.04479	-0.04037	0.21874	0.45720	0.08892
	0.6613	0.4746	0.8555	0.8658	0.3542	0.0427	0.7174
	19	20	19	20	20	20	19
lep0	0.46220	-0.32883	-0.01529	-0.21411	0.74770	0.48286	0.39393
	0.0828	0.2137	0.9569	0.4259	0.0009	0.0582	0.1463
	15	16	15	16	16	16	15
lep30	0.33778	0.08744	0.68478	-0.03931	0.67041	0.68978	0.44352
	0.2829	0.7870	0.0140	0.9035	0.0170	0.0131	0.1487
	12	12	12	12	12	12	12

Correlations Among Variables
OGTT 1 to DXA 1

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
lep60	-0.17242	0.55832	0.54269	0.35885	0.44296	0.46788	0.30571
	0.5921	0.0474	0.0553	0.2285	0.1295	0.1069	0.3097
	12	13	13	13	13	13	13
lep120	0.11029	-0.16878	0.08056	0.06468	0.54181	0.57678	0.50287
	0.6956	0.5321	0.7668	0.8119	0.0302	0.0193	0.0471
	15	16	16	16	16	16	16
weight	0.03163	0.10932	0.40802	0.11052	0.58521	0.47379	0.29858
	0.8977	0.6464	0.0829	0.6428	0.0067	0.0348	0.2144
	19	20	19	20	20	20	19
gluc0	1.00000	-0.29072	0.10182	-0.23941	0.62901	0.25395	0.03045
		0.2273	0.6877	0.3235	0.0039	0.2941	0.9045
	19	19	18	19	19	19	18
gluc30	-0.29072	1.00000	0.57483	0.49150	-0.24817	0.19009	0.33489
	0.2273		0.0100	0.0277	0.2914	0.4221	0.1611
	19	20	19	20	20	20	19
gluc60	0.10182	0.57483	1.00000	0.53478	0.11246	0.27887	0.43926
	0.6877	0.0100		0.0183	0.6467	0.2476	0.0599
	18	19	19	19	19	19	19
gluc120	-0.23941	0.49150	0.53478	1.00000	-0.08856	0.14779	0.16666
	0.3235	0.0277	0.0183		0.7104	0.5341	0.4953
	19	20	19	20	20	20	19
ins0	0.62901	-0.24817	0.11246	-0.08856	1.00000	0.38597	0.30025
	0.0039	0.2914	0.6467	0.7104		0.0928	0.2117
	19	20	19	20	20	20	19
ins30	0.25395	0.19009	0.27887	0.14779	0.38597	1.00000	0.32084
	0.2941	0.4221	0.2476	0.5341	0.0928		0.1805
	19	20	19	20	20	20	19
ins60	0.03045	0.33489	0.43926	0.16666	0.30025	0.32084	1.00000
	0.9045	0.1611	0.0599	0.4953	0.2117	0.1805	
	18	19	19	19	19	19	19
ins120	0.01457	-0.12038	0.05208	0.25570	0.53420	0.42625	0.46734
	0.9557	0.6454	0.8426	0.3219	0.0272	0.0880	0.0586
	17	17	17	17	17	17	17

Correlations Among Variables
OGTT 1 to DXA 1

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
bmcg	0.09389	0.00961	0.01995	-0.12827	0.52184	0.28677	-0.10138
	0.7022	0.9679	0.9354	0.5899	0.0183	0.2203	0.6796
	19	20	19	20	20	20	19
fatg	0.26960	-0.36964	-0.19826	-0.27237	0.69446	0.43587	0.03795
	0.2643	0.1087	0.4158	0.2453	0.0007	0.0547	0.8774
	19	20	19	20	20	20	19
leang	-0.09676	0.26376	0.49671	0.18595	0.29328	0.10043	0.10697
	0.6935	0.2612	0.0305	0.4325	0.2095	0.6736	0.6629
	19	20	19	20	20	20	19
totg	0.07662	0.01246	0.28188	0.00026	0.61810	0.32004	0.10008
	0.7552	0.9584	0.2423	0.9991	0.0037	0.1689	0.6835
	19	20	19	20	20	20	19
pctfat	0.24588	-0.39560	-0.29856	-0.30834	0.60204	0.41026	0.00341
	0.3102	0.0843	0.2144	0.1859	0.0050	0.0724	0.9889
	19	20	19	20	20	20	19

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
ratid	0.22369	-0.26892	-0.12865	-0.07796	-0.13861	-0.11530
	0.3881	0.2516	0.5888	0.7439	0.5600	0.6283
	17	20	20	20	20	20
trmt	0.45289	0.27951	0.68678	-0.03624	0.34608	0.69770
	0.0679	0.2327	0.0008	0.8794	0.1350	0.0006
	17	20	20	20	20	20
lep0	0.77775	0.38137	0.72599	-0.00487	0.38370	0.71323
	0.0017	0.1450	0.0015	0.9857	0.1423	0.0019
	13	16	16	16	16	16
lep30	0.54228	0.53657	0.75337	0.38098	0.68766	0.70377
	0.0848	0.0721	0.0047	0.2218	0.0135	0.0106
	11	12	12	12	12	12
lep60	-0.00558	0.25642	0.20773	0.34164	0.35437	0.11317
	0.9870	0.3978	0.4959	0.2533	0.2348	0.7128
	11	13	13	13	13	13

Correlations Among Variables
OGTT 1 to DXA 1

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
lep120	0.55486	0.20644	0.68455	-0.05020	0.30367	0.71160
	0.0395	0.4430	0.0034	0.8535	0.2529	0.0020
	14	16	16	16	16	16
weight	0.53457	0.77272	0.51530	0.80153	0.93254	0.34644
	0.0271	<.0001	0.0201	<.0001	<.0001	0.1346
	17	20	20	20	20	20
gluc0	0.01457	0.09389	0.26960	-0.09676	0.07662	0.24588
	0.9557	0.7022	0.2643	0.6935	0.7552	0.3102
	17	19	19	19	19	19
gluc30	-0.12038	0.00961	-0.36964	0.26376	0.01246	-0.39560
	0.6454	0.9679	0.1087	0.2612	0.9584	0.0843
	17	20	20	20	20	20
gluc60	0.05208	0.01995	-0.19826	0.49671	0.28188	-0.29856
	0.8426	0.9354	0.4158	0.0305	0.2423	0.2144
	17	19	19	19	19	19
gluc120	0.25570	-0.12827	-0.27237	0.18595	0.00026	-0.30834
	0.3219	0.5899	0.2453	0.4325	0.9991	0.1859
	17	20	20	20	20	20
ins0	0.53420	0.52184	0.69446	0.29328	0.61810	0.60204
	0.0272	0.0183	0.0007	0.2095	0.0037	0.0050
	17	20	20	20	20	20
ins30	0.42625	0.28677	0.43587	0.10043	0.32004	0.41026
	0.0880	0.2203	0.0547	0.6736	0.1689	0.0724
	17	20	20	20	20	20
ins60	0.46734	-0.10138	0.03795	0.10697	0.10008	0.00341
	0.0586	0.6796	0.8774	0.6629	0.6835	0.9889
	17	19	19	19	19	19
ins120	1.00000	0.34273	0.54080	0.09349	0.45254	0.49842
		0.1781	0.0250	0.7212	0.0682	0.0417
	17	17	17	17	17	17
bmcg	0.34273	1.00000	0.61073	0.66826	0.88563	0.48429
	0.1781		0.0042	0.0013	<.0001	0.0305
	17	20	20	20	20	20

Correlations Among Variables
OGTT 1 to DXA 1

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
fatg	0.54080	0.61073	1.00000	0.04343	0.58613	0.97874
	0.0250	0.0042		0.8557	0.0066	<.0001
	17	20	20	20	20	20
leang	0.09349	0.66826	0.04343	1.00000	0.83474	-0.15398
	0.7212	0.0013	0.8557		<.0001	0.5169
	17	20	20	20	20	20
totg	0.45254	0.88563	0.58613	0.83474	1.00000	0.41477
	0.0682	<.0001	0.0066	<.0001		0.0690
	17	20	20	20	20	20
pctfat	0.49842	0.48429	0.97874	-0.15398	0.41477	1.00000
	0.0417	0.0305	<.0001	0.5169	0.0690	
	17	20	20	20	20	20

Correlations Among Variables
DXA 1 to OGTT 2

The CORR Procedure

20 Variables: ratid trmt lep0 lep30 lep60 lep120 weight gluc0 gluc30 gluc60 gluc120 ins0 ins30 ins60 ins120 bmcg fatg leang totg pctfat

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
ratid	20	15.00000	8.85557	300.00000	1.00000	29.00000
trmt	20	1.50000	0.51299	30.00000	1.00000	2.00000
lep0	15	1.43786	0.45223	21.56789	0.80641	2.69970
lep30	12	1.34815	0.36963	16.17775	0.92064	1.98810
lep60	18	1.63558	0.52130	29.44043	0.84110	2.78460
lep120	16	2.11033	0.77930	33.76526	0.97476	4.01190
weight	20	190.94600	12.41382	3819	156.28000	209.53000
gluc0	20	102.25000	8.16201	2045	79.00000	115.00000
gluc30	19	189.89474	21.23125	3608	148.00000	237.00000
gluc60	19	206.21053	36.89411	3918	124.00000	301.00000
gluc120	19	165.10526	32.19713	3137	106.00000	228.00000
ins0	19	1.57057	0.63813	29.84078	0.37882	2.66280
ins30	19	2.29511	0.70842	43.60709	0.81409	3.55390
ins60	19	2.09443	0.55522	39.79410	1.15240	2.98650
ins120	19	1.89972	0.56284	36.09470	0.73220	2.77420
bmcg	20	6.05500	0.46394	121.10000	4.90000	6.90000
fatg	20	23.59500	6.20683	471.90000	16.20000	35.00000
leang	20	183.25500	10.89517	3665	153.70000	197.30000
totg	20	212.89000	14.26217	4258	174.80000	236.20000
pctfat	20	11.00500	2.46544	220.10000	7.50000	15.60000

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ratid	1.00000	0.05793	-0.12406	0.08195	-0.08959	0.09519	0.01573
		0.8083	0.6596	0.8001	0.7237	0.7258	0.9475
	20	20	15	12	18	16	20
trmt	0.05793	1.00000	0.16252	0.53164	0.48507	0.56278	0.44233
	0.8083		0.5628	0.0753	0.0413	0.0232	0.0508
	20	20	15	12	18	16	20
lep0	-0.12406	0.16252	1.00000	0.67920	0.60980	0.81873	-0.02597
	0.6596	0.5628		0.0308	0.0158	0.0003	0.9268
	15	15	15	10	15	14	15

Correlations Among Variables
DXA 1 to OGTT 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
lep30	0.08195	0.53164	0.67920	1.00000	0.91083	0.88457	0.25726
	0.8001	0.0753	0.0308		<.0001	0.0003	0.4195
	12	12	10	12	12	11	12
lep60	-0.08959	0.48507	0.60980	0.91083	1.00000	0.89041	0.47613
	0.7237	0.0413	0.0158	<.0001		<.0001	0.0458
	18	18	15	12	18	16	18
lep120	0.09519	0.56278	0.81873	0.88457	0.89041	1.00000	0.37061
	0.7258	0.0232	0.0003	0.0003	<.0001		0.1576
	16	16	14	11	16	16	16
weight	0.01573	0.44233	-0.02597	0.25726	0.47613	0.37061	1.00000
	0.9475	0.0508	0.9268	0.4195	0.0458	0.1576	
	20	20	15	12	18	16	20
gluc0	0.35680	0.25769	0.12473	0.49369	0.30276	0.25059	0.18754
	0.1225	0.2727	0.6578	0.1028	0.2220	0.3492	0.4285
	20	20	15	12	18	16	20
gluc30	0.04194	0.32162	0.02201	0.44224	0.32783	0.16708	0.24986
	0.8647	0.1794	0.9379	0.1500	0.1841	0.5363	0.3022
	19	19	15	12	18	16	19
gluc60	0.29132	0.63373	0.04126	0.42885	0.13008	0.26516	0.25681
	0.2262	0.0036	0.8839	0.1642	0.6069	0.3209	0.2885
	19	19	15	12	18	16	19
gluc120	0.40684	0.15455	0.12952	0.37288	0.07195	0.14882	-0.04044
	0.0839	0.5276	0.6455	0.2326	0.7766	0.5823	0.8694
	19	19	15	12	18	16	19
ins0	-0.12548	0.50094	0.32853	0.75372	0.85256	0.71266	0.54834
	0.6087	0.0289	0.2319	0.0046	<.0001	0.0019	0.0151
	19	19	15	12	18	16	19
ins30	-0.12850	0.21053	0.04845	0.30865	0.39978	0.20209	0.32708
	0.6001	0.3870	0.8639	0.3290	0.1002	0.4529	0.1717
	19	19	15	12	18	16	19
ins60	-0.03845	0.33177	0.05731	-0.02034	0.02158	-0.04608	0.11665
	0.8758	0.1652	0.8392	0.9500	0.9323	0.8654	0.6344
	19	19	15	12	18	16	19

Correlations Among Variables
DXA 1 to OGTT 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ins120	-0.10391	0.43926	-0.09470	0.45430	0.08491	0.11413	0.08724
	0.6721	0.0599	0.7371	0.1379	0.7376	0.6738	0.7225
	19	19	15	12	18	16	19
bmcg	-0.22291	0.23220	0.11395	-0.01666	0.32410	0.32185	0.86343
	0.3448	0.3246	0.6859	0.9590	0.1895	0.2241	<.0001
	20	20	15	12	18	16	20
fatg	-0.07287	0.78269	0.22876	0.45869	0.50810	0.58201	0.65484
	0.7601	<.0001	0.4122	0.1337	0.0313	0.0180	0.0017
	20	20	15	12	18	16	20
leang	0.02520	0.02401	-0.16418	0.03578	0.26982	0.15750	0.85945
	0.9160	0.9200	0.5587	0.9121	0.2789	0.5602	<.0001
	20	20	15	12	18	16	20
totg	-0.02092	0.36616	-0.00543	0.24661	0.42529	0.36799	0.96925
	0.9302	0.1123	0.9847	0.4397	0.0785	0.1608	<.0001
	20	20	15	12	18	16	20
pctfat	-0.06485	0.80940	0.24497	0.45553	0.46714	0.57727	0.48342
	0.7859	<.0001	0.3789	0.1367	0.0506	0.0192	0.0308
	20	20	15	12	18	16	20

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
ratid	0.35680	0.04194	0.29132	0.40684	-0.12548	-0.12850	-0.03845
	0.1225	0.8647	0.2262	0.0839	0.6087	0.6001	0.8758
	20	19	19	19	19	19	19
trmt	0.25769	0.32162	0.63373	0.15455	0.50094	0.21053	0.33177
	0.2727	0.1794	0.0036	0.5276	0.0289	0.3870	0.1652
	20	19	19	19	19	19	19
lep0	0.12473	0.02201	0.04126	0.12952	0.32853	0.04845	0.05731
	0.6578	0.9379	0.8839	0.6455	0.2319	0.8639	0.8392
	15	15	15	15	15	15	15
lep30	0.49369	0.44224	0.42885	0.37288	0.75372	0.30865	-0.02034
	0.1028	0.1500	0.1642	0.2326	0.0046	0.3290	0.9500
	12	12	12	12	12	12	12

Correlations Among Variables
DXA 1 to OGTT 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
lep60	0.30276	0.32783	0.13008	0.07195	0.85256	0.39978	0.02158
	0.2220	0.1841	0.6069	0.7766	<.0001	0.1002	0.9323
	18	18	18	18	18	18	18
lep120	0.25059	0.16708	0.26516	0.14882	0.71266	0.20209	-0.04608
	0.3492	0.5363	0.3209	0.5823	0.0019	0.4529	0.8654
	16	16	16	16	16	16	16
weight	0.18754	0.24986	0.25681	-0.04044	0.54834	0.32708	0.11665
	0.4285	0.3022	0.2885	0.8694	0.0151	0.1717	0.6344
	20	19	19	19	19	19	19
gluc0	1.00000	0.33997	0.42245	0.43194	0.39161	-0.11586	0.23018
		0.1544	0.0716	0.0648	0.0973	0.6367	0.3431
	20	19	19	19	19	19	19
gluc30	0.33997	1.00000	0.53572	0.49374	0.36935	0.47724	0.24355
	0.1544		0.0181	0.0317	0.1314	0.0388	0.3150
	19	19	19	19	18	19	19
gluc60	0.42245	0.53572	1.00000	0.48637	0.17694	-0.03523	0.20447
	0.0716	0.0181		0.0347	0.4824	0.8861	0.4011
	19	19	19	19	18	19	19
gluc120	0.43194	0.49374	0.48637	1.00000	0.03894	0.21616	0.52643
	0.0648	0.0317	0.0347		0.8781	0.3741	0.0206
	19	19	19	19	18	19	19
ins0	0.39161	0.36935	0.17694	0.03894	1.00000	0.36430	0.22636
	0.0973	0.1314	0.4824	0.8781		0.1372	0.3664
	19	18	18	18	19	18	18
ins30	-0.11586	0.47724	-0.03523	0.21616	0.36430	1.00000	0.44178
	0.6367	0.0388	0.8861	0.3741	0.1372		0.0583
	19	19	19	19	18	19	19
ins60	0.23018	0.24355	0.20447	0.52643	0.22636	0.44178	1.00000
	0.3431	0.3150	0.4011	0.0206	0.3664	0.0583	
	19	19	19	19	18	19	19
ins120	0.05209	0.37404	0.52512	0.40503	0.10375	0.37179	0.39330
	0.8323	0.1147	0.0210	0.0854	0.6820	0.1170	0.0957
	19	19	19	19	18	19	19

Correlations Among Variables
DXA 1 to OGTT 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
bmcg	-0.18173	0.00003	0.01766	-0.21909	0.26802	0.29925	-0.04050
	0.4432	0.9999	0.9428	0.3675	0.2673	0.2133	0.8692
	20	19	19	19	19	19	19
fatg	0.21165	0.22885	0.50114	-0.16261	0.61215	0.13425	0.06201
	0.3704	0.3460	0.0288	0.5060	0.0053	0.5837	0.8009
	20	19	19	19	19	19	19
leang	0.15129	0.11083	0.02614	0.02806	0.28897	0.36196	0.11130
	0.5243	0.6515	0.9154	0.9092	0.2302	0.1278	0.6501
	20	19	19	19	19	19	19
totg	0.20149	0.17866	0.22958	-0.05539	0.49629	0.33585	0.10701
	0.3943	0.4643	0.3444	0.8218	0.0307	0.1598	0.6628
	20	19	19	19	19	19	19
pctfat	0.17727	0.19025	0.50606	-0.19085	0.56639	0.05909	0.04316
	0.4547	0.4353	0.0271	0.4338	0.0115	0.8101	0.8607
	20	19	19	19	19	19	19

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
ratid	-0.10391	-0.22291	-0.07287	0.02520	-0.02092	-0.06485
	0.6721	0.3448	0.7601	0.9160	0.9302	0.7859
	19	20	20	20	20	20
trmt	0.43926	0.23220	0.78269	0.02401	0.36616	0.80940
	0.0599	0.3246	<.0001	0.9200	0.1123	<.0001
	19	20	20	20	20	20
lep0	-0.09470	0.11395	0.22876	-0.16418	-0.00543	0.24497
	0.7371	0.6859	0.4122	0.5587	0.9847	0.3789
	15	15	15	15	15	15
lep30	0.45430	-0.01666	0.45869	0.03578	0.24661	0.45553
	0.1379	0.9590	0.1337	0.9121	0.4397	0.1367
	12	12	12	12	12	12
lep60	0.08491	0.32410	0.50810	0.26982	0.42529	0.46714
	0.7376	0.1895	0.0313	0.2789	0.0785	0.0506
	18	18	18	18	18	18

Correlations Among Variables
DXA 1 to OGTT 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
lep120	0.11413	0.32185	0.58201	0.15750	0.36799	0.57727
	0.6738	0.2241	0.0180	0.5602	0.1608	0.0192
	16	16	16	16	16	16
weight	0.08724	0.86343	0.65484	0.85945	0.96925	0.48342
	0.7225	<.0001	0.0017	<.0001	<.0001	0.0308
	19	20	20	20	20	20
gluc0	0.05209	-0.18173	0.21165	0.15129	0.20149	0.17727
	0.8323	0.4432	0.3704	0.5243	0.3943	0.4547
	19	20	20	20	20	20
gluc30	0.37404	0.00003	0.22885	0.11083	0.17866	0.19025
	0.1147	0.9999	0.3460	0.6515	0.4643	0.4353
	19	19	19	19	19	19
gluc60	0.52512	0.01766	0.50114	0.02614	0.22958	0.50606
	0.0210	0.9428	0.0288	0.9154	0.3444	0.0271
	19	19	19	19	19	19
gluc120	0.40503	-0.21909	-0.16261	0.02806	-0.05539	-0.19085
	0.0854	0.3675	0.5060	0.9092	0.8218	0.4338
	19	19	19	19	19	19
ins0	0.10375	0.26802	0.61215	0.28897	0.49629	0.56639
	0.6820	0.2673	0.0053	0.2302	0.0307	0.0115
	18	19	19	19	19	19
ins30	0.37179	0.29925	0.13425	0.36196	0.33585	0.05909
	0.1170	0.2133	0.5837	0.1278	0.1598	0.8101
	19	19	19	19	19	19
ins60	0.39330	-0.04050	0.06201	0.11130	0.10701	0.04316
	0.0957	0.8692	0.8009	0.6501	0.6628	0.8607
	19	19	19	19	19	19
ins120	1.00000	-0.03398	0.15536	0.01693	0.07668	0.14613
		0.8902	0.5254	0.9451	0.7550	0.5505
	19	19	19	19	19	19
bmcg	-0.03398	1.00000	0.50566	0.83101	0.88739	0.33335
	0.8902		0.0229	<.0001	<.0001	0.1509
	19	20	20	20	20	20

Correlations Among Variables
DXA 1 to OGTT 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
fatg	0.15536	0.50566	1.00000	0.25731	0.64784	0.97500
	0.5254	0.0229		0.2734	0.0020	<.0001
	19	20	20	20	20	20
leang	0.01693	0.83101	0.25731	1.00000	0.90265	0.04229
	0.9451	<.0001	0.2734		<.0001	0.8595
	19	20	20	20	20	20
totg	0.07668	0.88739	0.64784	0.90265	1.00000	0.46713
	0.7550	<.0001	0.0020	<.0001		0.0378
	19	20	20	20	20	20
pctfat	0.14613	0.33335	0.97500	0.04229	0.46713	1.00000
	0.5505	0.1509	<.0001	0.8595	0.0378	
	19	20	20	20	20	20

Correlations Among Variables
OGTT 2 to DXA 2

The CORR Procedure

20 Variables: ratid trmt lep0 lep30 lep60 lep120 weight gluc0 gluc30 gluc60 gluc120 ins0 ins30 ins60 ins120 bmcg fatg leang totg pctfat .

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
ratid	20	15.00000	8.85557	300.00000	1.00000	29.00000
trmt	20	1.50000	0.51299	30.00000	1.00000	2.00000
lep0	15	1.43786	0.45223	21.56789	0.80641	2.69970
lep30	12	1.34815	0.36963	16.17775	0.92064	1.98810
lep60	18	1.63558	0.52130	29.44043	0.84110	2.78460
lep120	16	2.11033	0.77930	33.76526	0.97476	4.01190
weight	20	190.94600	12.41382	3819	156.28000	209.53000
gluc0	20	102.25000	8.16201	2045	79.00000	115.00000
gluc30	19	189.89474	21.23125	3608	148.00000	237.00000
gluc60	19	206.21053	36.89411	3918	124.00000	301.00000
gluc120	19	165.10526	32.19713	3137	106.00000	228.00000
ins0	19	1.57057	0.63813	29.84078	0.37882	2.66280
ins30	19	2.29511	0.70842	43.60709	0.81409	3.55390
ins60	19	2.09443	0.55522	39.79410	1.15240	2.98650
ins120	19	1.89972	0.56284	36.09470	0.73220	2.77420
bmcg	20	5.23500	0.42212	104.70000	4.20000	6.00000
fatg	20	21.33000	6.39392	426.60000	12.60000	41.10000
leang	20	161.84500	9.48359	3237	142.30000	175.70000
totg	20	188.41000	12.03621	3768	160.90000	209.50000
pctfat	20	11.24000	2.89689	224.80000	6.70000	19.70000

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ratid	1.00000	0.05793	-0.12406	0.08195	-0.08959	0.09519	0.01573
		0.8083	0.6596	0.8001	0.7237	0.7258	0.9475
	20	20	15	12	18	16	20
trmt	0.05793	1.00000	0.16252	0.53164	0.48507	0.56278	0.44233
	0.8083		0.5628	0.0753	0.0413	0.0232	0.0508
	20	20	15	12	18	16	20
lep0	-0.12406	0.16252	1.00000	0.67920	0.60980	0.81873	-0.02597
	0.6596	0.5628		0.0308	0.0158	0.0003	0.9268
	15	15	15	10	15	14	15

Correlations Among Variables
OGTT 2 to DXA 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
lep30	0.08195	0.53164	0.67920	1.00000	0.91083	0.88457	0.25726
	0.8001	0.0753	0.0308		<.0001	0.0003	0.4195
	12	12	10	12	12	11	12
lep60	-0.08959	0.48507	0.60980	0.91083	1.00000	0.89041	0.47613
	0.7237	0.0413	0.0158	<.0001		<.0001	0.0458
	18	18	15	12	18	16	18
lep120	0.09519	0.56278	0.81873	0.88457	0.89041	1.00000	0.37061
	0.7258	0.0232	0.0003	0.0003	<.0001		0.1576
	16	16	14	11	16	16	16
weight	0.01573	0.44233	-0.02597	0.25726	0.47613	0.37061	1.00000
	0.9475	0.0508	0.9268	0.4195	0.0458	0.1576	
	20	20	15	12	18	16	20
gluc0	0.35680	0.25769	0.12473	0.49369	0.30276	0.25059	0.18754
	0.1225	0.2727	0.6578	0.1028	0.2220	0.3492	0.4285
	20	20	15	12	18	16	20
gluc30	0.04194	0.32162	0.02201	0.44224	0.32783	0.16708	0.24986
	0.8647	0.1794	0.9379	0.1500	0.1841	0.5363	0.3022
	19	19	15	12	18	16	19
gluc60	0.29132	0.63373	0.04126	0.42885	0.13008	0.26516	0.25681
	0.2262	0.0036	0.8839	0.1642	0.6069	0.3209	0.2885
	19	19	15	12	18	16	19
gluc120	0.40684	0.15455	0.12952	0.37288	0.07195	0.14882	-0.04044
	0.0839	0.5276	0.6455	0.2326	0.7766	0.5823	0.8694
	19	19	15	12	18	16	19
ins0	-0.12548	0.50094	0.32853	0.75372	0.85256	0.71266	0.54834
	0.6087	0.0289	0.2319	0.0046	<.0001	0.0019	0.0151
	19	19	15	12	18	16	19
ins30	-0.12850	0.21053	0.04845	0.30865	0.39978	0.20209	0.32708
	0.6001	0.3870	0.8639	0.3290	0.1002	0.4529	0.1717
	19	19	15	12	18	16	19
ins60	-0.03845	0.33177	0.05731	-0.02034	0.02158	-0.04608	0.11665
	0.8758	0.1652	0.8392	0.9500	0.9323	0.8654	0.6344
	19	19	15	12	18	16	19

Correlations Among Variables
OGTT 2 to DXA 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ins120	-0.10391	0.43926	-0.09470	0.45430	0.08491	0.11413	0.08724
	0.6721	0.0599	0.7371	0.1379	0.7376	0.6738	0.7225
	19	19	15	12	18	16	19
bmcg	-0.26892	0.27951	0.04940	0.03298	0.35376	0.31345	0.82094
	0.2516	0.2327	0.8612	0.9190	0.1498	0.2371	<.0001
	20	20	15	12	18	16	20
fatg	-0.12865	0.68678	0.20710	0.58355	0.49120	0.53575	0.56707
	0.5888	0.0008	0.4589	0.0464	0.0384	0.0324	0.0091
	20	20	15	12	18	16	20
leang	-0.07796	-0.03624	0.02614	0.00175	0.24063	0.17948	0.75890
	0.7439	0.8794	0.9263	0.9957	0.3361	0.5060	0.0001
	20	20	15	12	18	16	20
totg	-0.13861	0.34608	0.13622	0.31436	0.43932	0.40594	0.92766
	0.5600	0.1350	0.6283	0.3197	0.0681	0.1187	<.0001
	20	20	15	12	18	16	20
pctfat	-0.11530	0.69770	0.18551	0.57672	0.45263	0.50264	0.41628
	0.6283	0.0006	0.5080	0.0496	0.0593	0.0472	0.0679
	20	20	15	12	18	16	20

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
ratid	0.35680	0.04194	0.29132	0.40684	-0.12548	-0.12850	-0.03845
	0.1225	0.8647	0.2262	0.0839	0.6087	0.6001	0.8758
	20	19	19	19	19	19	19
trmt	0.25769	0.32162	0.63373	0.15455	0.50094	0.21053	0.33177
	0.2727	0.1794	0.0036	0.5276	0.0289	0.3870	0.1652
	20	19	19	19	19	19	19
lep0	0.12473	0.02201	0.04126	0.12952	0.32853	0.04845	0.05731
	0.6578	0.9379	0.8839	0.6455	0.2319	0.8639	0.8392
	15	15	15	15	15	15	15
lep30	0.49369	0.44224	0.42885	0.37288	0.75372	0.30865	-0.02034
	0.1028	0.1500	0.1642	0.2326	0.0046	0.3290	0.9500
	12	12	12	12	12	12	12

Correlations Among Variables
OGTT 2 to DXA 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
lep60	0.30276	0.32783	0.13008	0.07195	0.85256	0.39978	0.02158
	0.2220	0.1841	0.6069	0.7766	<.0001	0.1002	0.9323
	18	18	18	18	18	18	18
lep120	0.25059	0.16708	0.26516	0.14882	0.71266	0.20209	-0.04608
	0.3492	0.5363	0.3209	0.5823	0.0019	0.4529	0.8654
	16	16	16	16	16	16	16
weight	0.18754	0.24986	0.25681	-0.04044	0.54834	0.32708	0.11665
	0.4285	0.3022	0.2885	0.8694	0.0151	0.1717	0.6344
	20	19	19	19	19	19	19
gluc0	1.00000	0.33997	0.42245	0.43194	0.39161	-0.11586	0.23018
		0.1544	0.0716	0.0648	0.0973	0.6367	0.3431
	20	19	19	19	19	19	19
gluc30	0.33997	1.00000	0.53572	0.49374	0.36935	0.47724	0.24355
	0.1544		0.0181	0.0317	0.1314	0.0388	0.3150
	19	19	19	19	18	19	19
gluc60	0.42245	0.53572	1.00000	0.48637	0.17694	-0.03523	0.20447
	0.0716	0.0181		0.0347	0.4824	0.8861	0.4011
	19	19	19	19	18	19	19
gluc120	0.43194	0.49374	0.48637	1.00000	0.03894	0.21616	0.52643
	0.0648	0.0317	0.0347		0.8781	0.3741	0.0206
	19	19	19	19	18	19	19
ins0	0.39161	0.36935	0.17694	0.03894	1.00000	0.36430	0.22636
	0.0973	0.1314	0.4824	0.8781		0.1372	0.3664
	19	18	18	18	19	18	18
ins30	-0.11586	0.47724	-0.03523	0.21616	0.36430	1.00000	0.44178
	0.6367	0.0388	0.8861	0.3741	0.1372		0.0583
	19	19	19	19	18	19	19
ins60	0.23018	0.24355	0.20447	0.52643	0.22636	0.44178	1.00000
	0.3431	0.3150	0.4011	0.0206	0.3664	0.0583	
	19	19	19	19	18	19	19
ins120	0.05209	0.37404	0.52512	0.40503	0.10375	0.37179	0.39330
	0.8323	0.1147	0.0210	0.0854	0.6820	0.1170	0.0957
	19	19	19	19	18	19	19

Correlations Among Variables
OGTT 2 to DXA 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
bmcg	-0.23029	0.01443	0.05025	-0.38417	0.37826	0.24483	-0.16599
	0.3287	0.9533	0.8381	0.1044	0.1103	0.3124	0.4970
	20	19	19	19	19	19	19
fatg	0.17654	0.31156	0.51902	-0.22814	0.60683	0.10199	-0.06540
	0.4565	0.1941	0.0228	0.3475	0.0059	0.6778	0.7902
	20	19	19	19	19	19	19
leang	-0.05625	-0.06360	-0.04719	-0.02272	0.12463	0.20995	-0.01242
	0.8138	0.7959	0.8479	0.9264	0.6112	0.3883	0.9598
	20	19	19	19	19	19	19
totg	0.04037	0.10844	0.22686	-0.14526	0.42723	0.22087	-0.04800
	0.8658	0.6586	0.3503	0.5529	0.0681	0.3635	0.8453
	20	19	19	19	19	19	19
pctfat	0.17407	0.31683	0.52967	-0.23893	0.58985	0.07243	-0.05687
	0.4630	0.1863	0.0197	0.3246	0.0079	0.7682	0.8171
	20	19	19	19	19	19	19

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
ratid	-0.10391	-0.26892	-0.12865	-0.07796	-0.13861	-0.11530
	0.6721	0.2516	0.5888	0.7439	0.5600	0.6283
	19	20	20	20	20	20
trmt	0.43926	0.27951	0.68678	-0.03624	0.34608	0.69770
	0.0599	0.2327	0.0008	0.8794	0.1350	0.0006
	19	20	20	20	20	20
lep0	-0.09470	0.04940	0.20710	0.02614	0.13622	0.18551
	0.7371	0.8612	0.4589	0.9263	0.6283	0.5080
	15	15	15	15	15	15
lep30	0.45430	0.03298	0.58355	0.00175	0.31436	0.57672
	0.1379	0.9190	0.0464	0.9957	0.3197	0.0496
	12	12	12	12	12	t2
lep60	0.08491	0.35376	0.49120	0.24063	0.43932	0.45263
	0.7376	0.1498	0.0384	0.3361	0.0681	0.0593
	18	18	18	18	18	18

Correlations Among Variables
OGTT 2 to DXA 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
lep120	0.11413	0.31345	0.53575	0.17948	0.40594	0.50264
	0.6738	0.2371	0.0324	0.5060	0.1187	0.0472
	16	16	16	16	16	16
weight	0.08724	0.82094	0.56707	0.75890	0.92766	0.41628
	0.7225	<.0001	0.0091	0.0001	<.0001	0.0679
	19	20	20	20	20	20
gluc0	0.05209	-0.23029	0.17654	-0.05625	0.04037	0.17407
	0.8323	0.3287	0.4565	0.8138	0.8658	0.4630
	19	20	20	20	20	20
gluc30	0.37404	0.01443	0.31156	-0.06360	0.10844	0.31683
	0.1147	0.9533	0.1941	0.7959	0.6586	0.1863
	19	19	19	19	19	19
gluc60	0.52512	0.05025	0.51902	-0.04719	0.22686	0.52967
	0.0210	0.8381	0.0228	0.8479	0.3503	0.0197
	19	19	19	19	19	19
gluc120	0.40503	-0.38417	-0.22814	-0.02272	-0.14526	-0.23893
	0.0854	0.1044	0.3475	0.9264	0.5529	0.3246
	19	19	19	19	19	19
ins0	0.10375	0.37826	0.60683	0.12463	0.42723	0.58985
	0.6820	0.1103	0.0059	0.6112	0.0681	0.0079
	18	19	19	19	19	19
ins30	0.37179	0.24483	0.10199	0.20995	0.22087	0.07243
	0.1170	0.3124	0.6778	0.3883	0.3635	0.7682
	19	19	19	19	19	19
ins60	0.39330	-0.16599	-0.06540	-0.01242	-0.04800	-0.05687
	0.0957	0.4970	0.7902	0.9598	0.8453	0.8171
	19	19	19	19	19	19
ins120	1.00000	0.05805	0.34151	-0.06562	0.12330	0.34546
		0.8134	0.1524	0.7895	0.6150	0.1474
	19	19	19	19	19	19
bmcg	0.05805	1.00000	0.61073	0.66826	0.88563	0.48429
	0.8134		0.0042	0.0013	<.0001	0.0305
	19	20	20	20	20	20

Correlations Among Variables
OGTT 2 to DXA 2

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
fatg	0.34151	0.61073	1.00000	0.04343	0.58613	0.97874
	0.1524	0.0042		0.8557	0.0066	<.0001
	19	20	20	20	20	20
leang	-0.06562	0.66826	0.04343	1.00000	0.83474	-0.15398
	0.7895	0.0013	0.8557		<.0001	0.5169
	19	20	20	20	20	20
totg	0.12330	0.88563	0.58613	0.83474	1.00000	0.41477
	0.6150	<.0001	0.0066	<.0001		0.0690
	19	20	20	20	20	20
pctfat	0.34546	0.48429	0.97874	-0.15398	0.41477	1.00000
	0.1474	0.0305	<.0001	0.5169	0.0690	
	19	20	20	20	20	20

Correlations Among Variables
DXA 2 to OGTT 3

The CORR Procedure

20 Variables: ratid trmt lep0 lep30 lep60 lep120 weight gluc0 gluc30 gluc60 gluc120 ins0 ins30 ins60 ins120 bmcg fatg leang totg pctfat

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
ratid	20	15.00000	8.85557	300.00000	1.00000	29.00000
trmt	20	1.50000	0.51299	30.00000	1.00000	2.00000
lep0	17	1.42148	0.46635	24.16524	0.85490	2.67470
lep30	16	1.39023	0.67548	22.24372	0.62688	2.92510
lep60	17	1.70877	0.68787	29.04903	0.67437	3.55810
lep120	16	2.12896	0.89508	34.06336	0.98636	3.80220
weight	19	211.68579	14.45317	4022	171.55000	233.16000
gluc0	18	110.83333	14.08065	1995	88.00000	141.00000
gluc30	17	181.94118	32.32737	3093	145.00000	246.00000
gluc60	17	191.23529	19.25659	3251	165.00000	235.00000
gluc120	17	174.76471	38.89654	2971	107.00000	249.00000
ins0	16	0.79545	0.40497	12.72713	0.13189	1.47860
ins30	16	1.65396	0.60033	26.46339	0.33167	2.48250
ins60	16	1.35270	0.47516	21.64321	0.43490	2.19300
ins120	16	1.27303	0.61559	20.36852	0.26565	2.10880
bmcg	20	6.05500	0.46394	121.10000	4.90000	6.90000
fatg	20	23.59500	6.20683	471.90000	16.20000	35.00000
leang	20	183.25500	10.89517	3665	153.70000	197.30000
totg	20	212.89000	14.26217	4258	174.80000	236.20000
pctfat	20	11.00500	2.46544	220.10000	7.50000	15.60000

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ratid	1.00000	0.05793	-0.24825	0.02493	-0.06704	0.01138	0.02508
		0.8083	0.3367	0.9270	0.7982	0.9666	0.9188
	20	20	17	16	17	16	19
trmt	0.05793	1.00000	0.50501	0.35540	0.69618	0.73439	0.45522
	0.8083		0.0387	0.1767	0.0019	0.0012	0.0502
	20	20	17	16	17	16	19
lep0	-0.24825	0.50501	1.00000	0.73715	0.77867	0.62967	0.52884
	0.3367	0.0387		0.0011	0.0002	0.0090	0.0291
	17	17	17	16	17	16	17

Correlations Among Variables
DXA 2 to OGTT 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
lep30	0.02493	0.35540	0.73715	1.00000	0.73355	0.54873	0.39345
	0.9270	0.1767	0.0011		0.0012	0.0342	0.1316
	16	16	16	16	16	15	16
lep60	-0.06704	0.69618	0.77867	0.73355	1.00000	0.81479	0.42613
	0.7982	0.0019	0.0002	0.0012		0.0001	0.0881
	17	17	17	16	17	16	17
lep120	0.01138	0.73439	0.62967	0.54873	0.81479	1.00000	0.45508
	0.9666	0.0012	0.0090	0.0342	0.0001		0.0765
	16	16	16	15	16	16	16
weight	0.02508	0.45522	0.52884	0.39345	0.42613	0.45508	1.00000
	0.9188	0.0502	0.0291	0.1316	0.0881	0.0765	
	19	19	17	16	17	16	19
gluc0	-0.12438	0.21788	0.26565	0.38312	0.37373	0.55427	-0.02290
	0.6229	0.3851	0.3027	0.1430	0.1395	0.0259	0.9281
	18	18	17	16	17	16	18
gluc30	-0.36149	-0.08068	-0.11302	0.10577	0.08089	0.03719	-0.27674
	0.1540	0.7582	0.6658	0.6966	0.7576	0.8912	0.2822
	17	17	17	16	17	16	17
gluc60	0.02973	0.20113	-0.18506	-0.13679	0.00427	0.13393	-0.11215
	0.9098	0.4389	0.4770	0.6135	0.9870	0.6209	0.6683
	17	17	17	16	17	16	17
gluc120	-0.12040	-0.15266	0.24786	0.35106	0.08921	0.20708	0.07688
	0.6453	0.5586	0.3375	0.1825	0.7335	0.4416	0.7693
	17	17	17	16	17	16	17
ins0	-0.01314	0.67116	0.68081	0.50295	0.69519	0.73950	0.76024
	0.9615	0.0044	0.0037	0.0560	0.0028	0.0016	0.0006
	16	16	16	15	16	15	16
ins30	-0.15126	0.39343	0.33322	0.06257	0.09372	0.11546	0.34590
	0.5760	0.1316	0.2072	0.8247	0.7299	0.6820	0.1894
	16	16	16	15	16	15	16
ins60	-0.31792	0.16410	0.29854	0.04303	0.32242	-0.08748	0.12551
	0.2301	0.5437	0.2614	0.8790	0.2233	0.7566	0.6432
	16	16	16	15	16	15	16

Correlations Among Variables
DXA 2 to OGTT 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ins120	-0.42642	0.27696	0.25819	-0.02105	0.20982	-0.07107	0.22782
	0.0995	0.2990	0.3343	0.9406	0.4354	0.8013	0.3961
	16	16	16	15	16	15	16
bmcg	-0.22291	0.23220	0.45255	0.26852	0.22043	0.07239	0.87665
	0.3448	0.3246	0.0681	0.3146	0.3952	0.7899	<.0001
	20	20	17	16	17	16	19
fatg	-0.07287	0.78269	0.55902	0.43461	0.69232	0.69827	0.63566
	0.7601	<.0001	0.0197	0.0925	0.0021	0.0026	0.0034
	20	20	17	16	17	16	19
leang	0.02520	0.02401	0.34548	0.24002	0.13414	-0.01185	0.89274
	0.9160	0.9200	0.1744	0.3706	0.6078	0.9653	<.0001
	20	20	17	16	17	16	19
totg	-0.02092	0.36616	0.50850	0.38097	0.39915	0.35543	0.98817
	0.9302	0.1123	0.0371	0.1454	0.1125	0.1767	<.0001
	20	20	17	16	17	16	19
pctfat	-0.06485	0.80940	0.50117	0.38228	0.68066	0.71049	0.45969
	0.7859	<.0001	0.0404	0.1439	0.0026	0.0020	0.0477
	20	20	17	16	17	16	19

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
ratid	-0.12438	-0.36149	0.02973	-0.12040	-0.01314	-0.15126	-0.31792
	0.6229	0.1540	0.9098	0.6453	0.9615	0.5760	0.2301
	18	17	17	17	16	16	16
trmt	0.21788	-0.08068	0.20113	-0.15266	0.67116	0.39343	0.16410
	0.3851	0.7582	0.4389	0.5586	0.0044	0.1316	0.5437
	18	17	17	17	16	16	16
lep0	0.26565	-0.11302	-0.18506	0.24786	0.68081	0.33322	0.29854
	0.3027	0.6658	0.4770	0.3375	0.0037	0.2072	0.2614
	17	17	17	17	16	16	16
lep30	0.38312	0.10577	-0.13679	0.35106	0.50295	0.06257	0.04303
	0.1430	0.6966	0.6135	0.1825	0.0560	0.8247	0.8790
	16	16	16	16	15	15	15

Correlations Among Variables
DXA 2 to OGTT 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
lep60	0.37373	0.08089	0.00427	0.08921	0.69519	0.09372	0.32242
	0.1395	0.7576	0.9870	0.7335	0.0028	0.7299	0.2233
	17	17	17	17	16	16	16
lep120	0.55427	0.03719	0.13393	0.20708	0.73950	0.11546	-0.08748
	0.0259	0.8912	0.6209	0.4416	0.0016	0.6820	0.7566
	16	16	16	16	15	15	15
weight	-0.02290	-0.27674	-0.11215	0.07688	0.76024	0.34590	0.12551
	0.9281	0.2822	0.6683	0.7693	0.0006	0.1894	0.6432
	18	17	17	17	16	16	16
gluc0	1.00000	0.49588	0.67358	0.66229	0.22850	-0.00611	-0.53920
		0.0429	0.0030	0.0038	0.3946	0.9821	0.0311
	18	17	17	17	16	16	16
gluc30	0.49588	1.00000	0.57350	0.12574	-0.20228	-0.37986	-0.02393
	0.0429		0.0161	0.6306	0.4525	0.1467	0.9299
	17	17	17	17	16	16	16
gluc60	0.67358	0.57350	1.00000	0.42906	-0.04320	0.05038	-0.27462
	0.0030	0.0161		0.0857	0.8738	0.8530	0.3033
	17	17	17	17	16	16	16
gluc120	0.66229	0.12574	0.42906	1.00000	0.23383	0.14115	-0.52210
	0.0038	0.6306	0.0857		0.3834	0.6021	0.0380
	17	17	17	17	16	16	16
ins0	0.22850	-0.20228	-0.04320	0.23383	1.00000	0.18136	0.09578
	0.3946	0.4525	0.8738	0.3834		0.5015	0.7242
	16	16	16	16	16	16	16
ins30	-0.00611	-0.37986	0.05038	0.14115	0.18136	1.00000	0.08613
	0.9821	0.1467	0.8530	0.6021	0.5015		0.7511
	16	16	16	16	16	16	16
ins60	-0.53920	-0.02393	-0.27462	-0.52210	0.09578	0.08613	1.00000
	0.0311	0.9299	0.3033	0.0380	0.7242	0.7511	
	16	16	16	16	16	16	16
ins120	-0.22321	-0.06742	-0.15626	-0.32216	0.02443	0.46298	0.62699
	0.4060	0.8041	0.5633	0.2237	0.9284	0.0709	0.0093
	16	16	16	16	16	16	16

Correlations Among Variables
DXA 2 to OGTT 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
bmcg	-0.30266	-0.32987	-0.29101	0.02092	0.57071	0.39041	0.31493
	0.2222	0.1960	0.2571	0.9365	0.0210	0.1349	0.2348
	18	17	17	17	16	16	16
fatg	0.11448	-0.23669	-0.11828	-0.05989	0.82048	0.31060	0.17464
	0.6510	0.3604	0.6512	0.8194	<.0001	0.2416	0.5177
	18	17	17	17	16	16	16
leang	-0.11213	-0.25668	-0.13157	0.14549	0.51733	0.26621	0.09148
	0.6578	0.3200	0.6147	0.5774	0.0401	0.3190	0.7362
	18	17	17	17	16	16	16
totg	-0.04473	-0.30089	-0.15740	0.08316	0.74595	0.33952	0.15251
	0.8601	0.2406	0.5463	0.7510	0.0009	0.1982	0.5728
	18	17	17	17	16	16	16
pctfat	0.14307	-0.19877	-0.09637	-0.10810	0.74015	0.28743	0.14357
	0.5712	0.4444	0.7129	0.6796	0.0010	0.2804	0.5958
	18	17	17	17	16	16	16

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
ratid	-0.42642	-0.22291	-0.07287	0.02520	-0.02092	-0.06485
	0.0995	0.3448	0.7601	0.9160	0.9302	0.7859
	16	20	20	20	20	20
trmt	0.27696	0.23220	0.78269	0.02401	0.36616	0.80940
	0.2990	0.3246	<.0001	0.9200	0.1123	<.0001
	16	20	20	20	20	20
lep0	0.25819	0.45255	0.55902	0.34548	0.50850	0.50117
	0.3343	0.0681	0.0197	0.1744	0.0371	0.0404
	16	17	17	17	17	17
lep30	-0.02105	0.26852	0.43461	0.24002	0.38097	0.38228
	0.9406	0.3146	0.0925	0.3706	0.1454	0.1439
	15	16	16	16	16	16
lep60	0.20982	0.22043	0.69232	0.13414	0.39915	0.68066
	0.4354	0.3952	0.0021	0.6078	0.1125	0.0026
	16	17	17	17	17	17

Correlations Among Variables
DXA 2 to OGTT 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
lep120	-0.07107	0.07239	0.69827	-0.01185	0.35543	0.71049
	0.8013	0.7899	0.0026	0.9653	0.1767	0.0020
	15	16	16	16	16	16
weight	0.22782	0.87665	0.63566	0.89274	0.98817	0.45969
	0.3961	<.0001	0.0034	<.0001	<.0001	0.0477
	16	19	19	19	19	19
gluc0	-0.22321	-0.30266	0.11448	-0.11213	-0.04473	0.14307
	0.4060	0.2222	0.6510	0.6578	0.8601	0.5712
	16	18	18	18	18	18
gluc30	-0.06742	-0.32987	-0.23669	-0.25668	-0.30089	-0.19877
	0.8041	0.1960	0.3604	0.3200	0.2406	0.4444
	16	17	17	17	17	17
gluc60	-0.15626	-0.29101	-0.11828	-0.13157	-0.15740	-0.09637
	0.5633	0.2571	0.6512	0.6147	0.5463	0.7129
	16	17	17	17	17	17
gluc120	-0.32216	0.02092	-0.05989	0.14549	0.08316	-0.10810
	0.2237	0.9365	0.8194	0.5774	0.7510	0.6796
	16	17	17	17	17	17
ins0	0.02443	0.57071	0.82048	0.51733	0.74595	0.74015
	0.9284	0.0210	<.0001	0.0401	0.0009	0.0010
	16	16	16	16	16	16
ins30	0.46298	0.39041	0.31060	0.26621	0.33952	0.28743
	0.0709	0.1349	0.2416	0.3190	0.1982	0.2804
	16	16	16	16	16	16
ins60	0.62699	0.31493	0.17464	0.09148	0.15251	0.14357
	0.0093	0.2348	0.5177	0.7362	0.5728	0.5958
	16	16	16	16	16	16
ins120	1.00000	0.28486	0.29435	0.17557	0.26368	0.27902
		0.2849	0.2684	0.5154	0.3237	0.2953
	16	16	16	16	16	16
bmcg	0.28486	1.00000	0.50566	0.83101	0.88739	0.33335
	0.2849		0.0229	<.0001	<.0001	0.1509
	16	20	20	20	20	20

Correlations Among Variables
DXA 2 to OGTT 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
fatg	0.29435	0.50566	1.00000	0.25731	0.64784	0.97500
	0.2684	0.0229		0.2734	0.0020	<.0001
	16	20	20	20	20	20
leang	0.17557	0.83101	0.25731	1.00000	0.90265	0.04229
	0.5154	<.0001	0.2734		<.0001	0.8595
	16	20	20	20	20	20
totg	0.26368	0.88739	0.64784	0.90265	1.00000	0.46713
	0.3237	<.0001	0.0020	<.0001		0.0378
	16	20	20	20	20	20
pctfat	0.27902	0.33335	0.97500	0.04229	0.46713	1.00000
	0.2953	0.1509	<.0001	0.8595	0.0378	
	16	20	20	20	20	20

Correlations Among Variables

OGTT 3 to DXA 3

The CORR Procedure

20 Variables: ratid trmt lep0 lep30 lep60 lep120 weight gluc0 gluc30 gluc60 gluc120 ins0 ins30 ins60 ins120 bmcg fatg leang totg pctfat

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
ratid	20	15.00000	8.85557	300.00000	1.00000	29.00000
trmt	20	1.50000	0.51299	30.00000	1.00000	2.00000
lep0	17	1.42148	0.46635	24.16524	0.85490	2.67470
lep30	16	1.39023	0.67548	22.24372	0.62688	2.92510
lep60	17	1.70877	0.68787	29.04903	0.67437	3.55810
lep120	16	2.12896	0.89508	34.06336	0.98636	3.80220
weight	19	211.68579	14.45317	4022	171.55000	233.16000
gluc0	18	110.83333	14.08065	1995	88.00000	141.00000
gluc30	17	181.94118	32.32737	3093	145.00000	246.00000
gluc60	17	191.23529	19.25659	3251	165.00000	235.00000
gluc120	17	174.76471	38.89654	2971	107.00000	249.00000
ins0	16	0.79545	0.40497	12.72713	0.13189	1.47860
ins30	16	1.65396	0.60033	26.46339	0.33167	2.48250
ins60	16	1.35270	0.47516	21.64321	0.43490	2.19300
ins120	16	1.27303	0.61559	20.36852	0.26565	2.10880
bmcg	19	6.74211	0.54090	128.10000	5.20000	7.80000
fatg	19	24.86316	7.13631	472.40000	14.80000	38.60000
leang	19	192.87895	11.77793	3665	164.70000	208.20000
totg	19	224.46842	15.03308	4265	184.70000	246.50000
pctfat	19	11.01053	2.74568	209.20000	7.50000	15.80000

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ratid	1.00000	0.05793	-0.24825	0.02493	-0.06704	0.01138	0.02508
		0.8083	0.3367	0.9270	0.7982	0.9666	0.9188
	20	20	17	16	17	16	19
trmt	0.05793	1.00000	0.50501	0.35540	0.69618	0.73439	0.45522
	0.8083		0.0387	0.1767	0.0019	0.0012	0.0502
	20	20	17	16	17	16	19
lep0	-0.24825	0.50501	1.00000	0.73715	0.77867	0.62967	0.52884
	0.3367	0.0387		0.0011	0.0002	0.0090	0.0291
	17	17	17	16	17	16	17

Correlations Among Variables
OGTT 3 to DXA 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under HO: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
lep30	0.02493	0.35540	0.73715	1.00000	0.73355	0.54873	0.39345
	0.9270	0.1767	0.0011		0.0012	0.0342	0.1316
	16	16	16	16	16	15	16
lep60	-0.06704	0.69618	0.77867	0.73355	1.00000	0.81479	0.42613
	0.7982	0.0019	0.0002	0.0012		0.0001	0.0881
	17	17	17	16	17	16	17
lep120	0.01138	0.73439	0.62967	0.54873	0.81479	1.00000	0.45508
	0.9666	0.0012	0.0090	0.0342	0.0001		0.0765
	16	16	16	15	16	16	16
weight	0.02508	0.45522	0.52884	0.39345	0.42613	0.45508	1.00000
	0.9188	0.0502	0.0291	0.1316	0.0881	0.0765	
	19	19	17	16	17	16	19
gluc0	-0.12438	0.21788	0.26565	0.38312	0.37373	0.55427	-0.02290
	0.6229	0.3851	0.3027	0.1430	0.1395	0.0259	0.9281
	18	18	17	16	17	16	18
gluc30	-0.36149	-0.08068	-0.11302	0.10577	0.08089	0.03719	-0.27674
	0.1540	0.7582	0.6658	0.6966	0.7576	0.8912	0.2822
	17	17	17	16	17	16	17
gluc60	0.02973	0.20113	-0.18506	-0.13679	0.00427	0.13393	-0.11215
	0.9098	0.4389	0.4770	0.6135	0.9870	0.6209	0.6683
	17	17	17	16	17	16	17
gluc120	-0.12040	-0.15266	0.24786	0.35106	0.08921	0.20708	0.07688
	0.6453	0.5586	0.3375	0.1825	0.7335	0.4416	0.7693
	17	17	17	16	17	16	17
ins0	-0.01314	0.67116	0.68081	0.50295	0.69519	0.73950	0.76024
	0.9615	0.0044	0.0037	0.0560	0.0028	0.0016	0.0006
	16	16	16	15	16	15	16
ins30	-0.15126	0.39343	0.33322	0.06257	0.09372	0.11546	0.34590
	0.5760	0.1316	0.2072	0.8247	0.7299	0.6820	0.1894
	16	16	16	15	16	15	16
ins60	-0.31792	0.16410	0.29854	0.04303	0.32242	-0.08748	0.12551
	0.2301	0.5437	0.2614	0.8790	0.2233	0.7566	0.6432
	16	16	16	15	16	15	16

Correlations Among Variables
OGTT 3 to DXA 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ratid	trmt	lep0	lep30	lep60	lep120	weight
ins120	-0.42642	0.27696	0.25819	-0.02105	0.20982	-0.07107	0.22782
	0.0995	0.2990	0.3343	0.9406	0.4354	0.8013	0.3961
	16	16	16	15	16	15	16
bmcg	-0.11803	0.23605	0.44750	0.25577	0.32939	0.08616	0.89134
	0.6304	0.3306	0.0717	0.3390	0.1967	0.7510	<.0001
	19	19	17	16	17	16	19
fatg	0.01095	0.79624	0.63343	0.52511	0.75546	0.71905	0.67155
	0.9645	<.0001	0.0063	0.0367	0.0005	0.0017	0.0016
	19	19	17	16	17	16	19
leang	0.01984	-0.06151	0.17963	0.10932	-0.03455	-0.13417	0.78277
	0.9358	0.8025	0.4903	0.6869	0.8953	0.6203	<.0001
	19	19	17	16	17	16	19
totg	0.01706	0.33726	0.44200	0.35099	0.34101	0.32692	0.96273
	0.9447	0.1579	0.0757	0.1825	0.1804	0.2165	<.0001
	19	19	17	16	17	16	19
pctfat	0.02977	0.82415	0.61173	0.50865	0.77760	0.73992	0.52934
	0.9037	<.0001	0.0091	0.0442	0.0002	0.0010	0.0198
	19	19	17	16	17	16	19

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
ratid	-0.12438	-0.36149	0.02973	-0.12040	-0.01314	-0.15126	-0.31792
	0.6229	0.1540	0.9098	0.6453	0.9615	0.5760	0.2301
	18	17	17	17	16	16	16
trmt	0.21788	-0.08068	0.20113	-0.15266	0.67116	0.39343	0.16410
	0.3851	0.7582	0.4389	0.5586	0.0044	0.1316	0.5437
	18	17	17	17	16	16	16
lep0	0.26565	-0.11302	-0.18506	0.24786	0.68081	0.33322	0.29854
	0.3027	0.6658	0.4770	0.3375	0.0037	0.2072	0.2614
	17	17	17	17	16	16	16
lep30	0.38312	0.10577	-0.13679	0.35106	0.50295	0.06257	0.04303
	0.1430	0.6966	0.6135	0.1825	0.0560	0.8247	0.8790
	16	16	16	16	15	15	15

Correlations Among Variables
OGTT 3 to DXA 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
lep60	0.37373	0.08089	0.00427	0.08921	0.69519	0.09372	0.32242
	0.1395	0.7576	0.9870	0.7335	0.0028	0.7299	0.2233
	17	17	17	17	16	16	16
lep120	0.55427	0.03719	0.13393	0.20708	0.73950	0.11546	-0.08748
	0.0259	0.8912	0.6209	0.4416	0.0016	0.6820	0.7566
	16	16	16	16	15	15	15
weight	-0.02290	-0.27674	-0.11215	0.07688	0.76024	0.34590	0.12551
	0.9281	0.2822	0.6683	0.7693	0.0006	0.1894	0.6432
	18	17	17	17	16	16	16
gluc0	1.00000	0.49588	0.67358	0.66229	0.22850	-0.00611	-0.53920
		0.0429	0.0030	0.0038	0.3946	0.9821	0.0311
	18	17	17	17	16	16	16
gluc30	0.49588	1.00000	0.57350	0.12574	-0.20228	-0.37986	-0.02393
	0.0429		0.0161	0.6306	0.4525	0.1467	0.9299
	17	17	17	17	16	16	16
gluc60	0.67358	0.57350	1.00000	0.42906	-0.04320	0.05038	-0.27462
	0.0030	0.0161		0.0857	0.8738	0.8530	0.3033
	17	17	17	17	16	16	16
gluc120	0.66229	0.12574	0.42906	1.00000	0.23383	0.14115	-0.52210
	0.0038	0.6306	0.0857		0.3834	0.6021	0.0380
	17	17	17	17	16	16	16
ins0	0.22850	-0.20228	-0.04320	0.23383	1.00000	0.18136	0.09578
	0.3946	0.4525	0.8738	0.3834		0.5015	0.7242
	16	16	16	16	16	16	16
ins30	-0.00611	-0.37986	0.05038	0.14115	0.18136	1.00000	0.08613
	0.9821	0.1467	0.8530	0.6021	0.5015		0.7511
	16	16	16	16	16	16	16
ins60	-0.53920	-0.02393	-0.27462	-0.52210	0.09578	0.08613	1.00000
	0.0311	0.9299	0.3033	0.0380	0.7242	0.7511	
	16	16	16	16	16	16	16
ins120	-0.22321	-0.06742	-0.15626	-0.32216	0.02443	0.46298	0.62699
	0.4060	0.8041	0.5633	0.2237	0.9284	0.0709	0.0093
	16	16	16	16	16	16	16

Correlations Among Variables
OGTT 3 to DXA 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	gluc0	gluc30	gluc60	gluc120	ins0	ins30	ins60
bmcg	-0.21170	-0.23701	-0.20845	-0.07037	0.59290	0.33728	0.39444
	0.3990	0.3597	0.4220	0.7884	0.0155	0.2014	0.1306
	18	17	17	17	16	16	16
fatg	0.04262	-0.27623	-0.19949	-0.02396	0.89242	0.20519	0.22858
	0.8667	0.2832	0.4427	0.9273	<.0001	0.4459	0.3945
	18	17	17	17	16	16	16
leang	-0.08617	-0.27128	-0.10043	0.07003	0.37527	0.34743	0.00890
	0.7339	0.2922	0.7013	0.7894	0.1521	0.1873	0.9739
	18	17	17	17	16	16	16
totg	-0.05404	-0.33378	-0.17453	0.03575	0.70791	0.35572	0.12839
	0.8313	0.1904	0.5029	0.8916	0.0022	0.1763	0.6356
	18	17	17	17	16	16	16
pctfat	0.04031	-0.23495	-0.19101	-0.06131	0.85807	0.16158	0.22853
	0.8738	0.3640	0.4627	0.8152	<.0001	0.5499	0.3946
	18	17	17	17	16	16	16

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
ratid	-0.42642	-0.11803	0.01095	0.01984	0.01706	0.02977
	0.0995	0.6304	0.9645	0.9358	0.9447	0.9037
	16	19	19	19	19	19
trmt	0.27696	0.23605	0.79624	-0.06151	0.33726	0.82415
	0.2990	0.3306	<.0001	0.8025	0.1579	<.0001
	16	19	19	19	19	19
lep0	0.25819	0.44750	0.63343	0.17963	0.44200	0.61173
	0.3343	0.0717	0.0063	0.4903	0.0757	0.0091
	16	17	17	17	17	17
lep30	-0.02105	0.25577	0.52511	0.10932	0.35099	0.50865
	0.9406	0.3390	0.0367	0.6869	0.1825	0.0442
	15	16	16	16	16	16
lep60	0.20982	0.32939	0.75546	-0.03455	0.34101	0.77760
	0.4354	0.1967	0.0005	0.8953	0.1804	0.0002
	16	17	17	17	17	17

Correlations Among Variables
OGTT 3 to DXA 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under HO: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
lep120	-0.07107	0.08616	0.71905	-0.13417	0.32692	0.73992
	0.8013	0.7510	0.0017	0.6203	0.2165	0.0010
	15	16	16	16	16	16
weight	0.22782	0.89134	0.67155	0.78277	0.96273	0.52934
	0.3961	<.0001	0.0016	<.0001	<.0001	0.0198
	16	19	19	19	19	19
gluc0	-0.22321	-0.21170	0.04262	-0.08617	-0.05404	0.04031
	0.4060	0.3990	0.8667	0.7339	0.8313	0.8738
	16	18	18	18	18	18
gluc30	-0.06742	-0.23701	-0.27623	-0.27128	-0.33378	-0.23495
	0.8041	0.3597	0.2832	0.2922	0.1904	0.3640
	16	17	17	17	17	17
gluc60	-0.15626	-0.20845	-0.19949	-0.10043	-0.17453	-0.19101
	0.5633	0.4220	0.4427	0.7013	0.5029	0.4627
	16	17	17	17	17	17
gluc120	-0.32216	-0.07037	-0.02396	0.07003	0.03575	-0.06131
	0.2237	0.7884	0.9273	0.7894	0.8916	0.8152
	16	17	17	17	17	17
ins0	0.02443	0.59290	0.89242	0.37527	0.70791	0.85807
	0.9284	0.0155	<.0001	0.1521	0.0022	<.0001
	16	16	16	16	16	16
ins30	0.46298	0.33728	0.20519	0.34743	0.35572	0.16158
	0.0709	0.2014	0.4459	0.1873	0.1763	0.5499
	16	16	16	16	16	16
ins60	0.62699	0.39444	0.22858	0.00890	0.12839	0.22853
	0.0093	0.1306	0.3945	0.9739	0.6356	0.3946
	16	16	16	16	16	16
ins120	1.00000	0.40102	0.24575	0.15581	0.24071	0.23455
		0.1237	0.3589	0.5645	0.3692	0.3819
	16	16	16	16	16	16
bmcg	0.40102	1.00000	0.50632	0.82484	0.92143	0.35057
	0.1237		0.0270	<.0001	<.0001	0.1411
	16	19	19	19	19	19

Correlations Among Variables
OGTT 3 to DXA 3

The CORR Procedure

Pearson Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

	ins120	bmcg	fatg	leang	totg	pctfat
fatg	0.24575	0.50632	1.00000	0.13189	0.59524	0.97929
	0.3589	0.0270		0.5904	0.0072	<.0001
	16	19	19	19	19	19
leang	0.15581	0.82484	0.13189	1.00000	0.87490	-0.06150
	0.5645	<.0001	0.5904		<.0001	0.8025
	16	19	19	19	19	19
totg	0.24071	0.92143	0.59524	0.87490	1.00000	0.42852
	0.3692	<.0001	0.0072	<.0001		0.0672
	16	19	19	19	19	19
pctfat	0.23455	0.35057	0.97929	-0.06150	0.42852	1.00000
	0.3819	0.1411	<.0001	0.8025	0.0672	
	16	19	19	19	19	19

VITA 2

Jackie L. Brown

Candidate for the Degree of

Master of Science

Thesis: EFFECT OF HIGH-FAT DIET ON BODY COMPOSITION AND HORMONE RESPONSES TO GLUCOSE TOLERANCE TESTS IN GROWING RATS

Major Field: Nutritional Sciences

Biographical:

Education: Graduated from Muncie Southside High School, Muncie , Indiana, in June 1988; received Bachelor of Science degree in Nutrition and Food Management with an option in dietetics, Oregon State University, Corvallis, Oregon in June 2000.
Completed the requirements for the Master of Science degree with a major in Nutritional Sciences at Oklahoma State University in August, 2002.

Experience: Volunteered as a nutrition educator in a residential drug and alcohol treatment center; volunteered as an assistant to a school district administrative dietitian; employed by Oregon State University Nutrition and Food Management Department as a food science web page editor; employed by Oklahoma State University Department of Nutritional Sciences as a graduate research and teaching assistant.

Professional Memberships: American Dietetic Association, Oklahoma Dietetic Association, Oregon Dietetic Association.