The Effect of Liposuction and Diet on Ghrelin, Adiponectin, and Leptin Levels in Obese Zucker Rats

Jeffrey E. Schreiber, M.D.
Navin K. Singh, M.D.
Michele A. Shermak, M.D.

Baltimore, Md.

Background: The fat-regulating hormones, adiponectin, ghrelin, and leptin, have been studied extensively with the hope that some therapeutic modality might be gleaned from their augmentation or blockade. The authors studied levels of ghrelin, adiponectin, and leptin after liposuction in obese male Zucker rats. In addition, they altered the fat and carbohydrate content of the rats' postoperative diets to determine whether diet affects hormonal levels and/or liposuction outcome.

Methods: Thirty-five male, obese Zucker rats were divided into four experimental groups. Group I ($n = 10$) was fed a low-fat/low-carbohydrate diet; group II ($n = 10$) was fed a regular chow diet; and group III ($n = 10$) was fed a high-fat/high-carbohydrate diet. Five additional rats served as the baseline, unoperated group. The experimental rats underwent subcutaneous liposuction, and for 6 weeks they were then fed their experimental diets starting on day 0. Experimental rats were euthanized on day 42 and blood was sampled for hormonal, triglyceride, and cholesterol levels.

Results: Triglyceride levels were significantly higher in the high-fat/high-carbohydrate group compared with the regular chow and low-fat/low-carbohydrate groups, indicating an effect of diet on systemic circulation after liposuction. Ghrelin levels decreased significantly and leptin levels demonstrated an increasing trend after liposuction. Adiponectin levels did not demonstrate any change with alteration in diet or liposuction.

Conclusions: Liposuction may prove to offer patients medically therapeutic benefits through hormonal alterations. After liposuction, diet plays an important role in weight gain. (*Plast. Reconstr. Surg.* 117: 1829, 2006.)

Obesity is a severely disabling and costly disease that has gained widespread attention.[1] Currently, 64.5 percent of adults in the United States are overweight (body mass index ≥ 25), and 30.5 percent are obese, defined medically as a state of increased body weight of sufficient magnitude to produce adverse health consequences, or body mass index greater than or equal to 30.[2–4] Obesity is increasing in prevalence and significantly increases the risk for disorders such as hypertension, dyslipidemia, non–insulin-dependent diabetes mellitus, coronary artery disease, stroke, gallbladder disease, gastroesophageal reflux disease, hypercholesterolemia, osteoarthritis, obstructive sleep apnea, and cancer.[5–11] Data from the American Obesity Association indicates that obesity is a contributing cause in at least 300,000 deaths per year.[2] Obesity is a problem that plagues our society and drains our medical system.

Because of the importance of obesity as a disease, researchers are increasingly focusing their efforts on studying mediators of fat metabolism, including hormones that affect fat synthesis or catabolism. Adiponectin, ghrelin, and leptin are such hormones, and their individual pathways and effects have been studied with the hope that a therapeutic modality might be gleaned from augmentation or blockade of the hormone in question.

Adiponectin is an adipocytokine that influences insulin sensitivity and plays a role in cardiac disease.[12] Adiponectin is found in adipocytes.[4] When adiponectin levels are low, insulin resistance is high, and type 2 diabetes

From the Division of Plastic Surgery, The Johns Hopkins Medical Institutions.
Received for publication September 13, 2004; revised January 23, 2005.

DOI: 10.1097/01.prs.0000209966.11255.4f

commonly results. Low adiponectin levels have also been associated with an increased risk for coronary artery disease. High levels of adiponectin, as seen with weight loss, can lead to higher levels of insulin sensitivity, alleviation of diabetic symptoms, and a better cardiac profile.[13,14]

Ghrelin is one of the more exciting hormones discovered, as it is the only hormone found to stimulate food intake in humans.[15] Endogenous ghrelin production has been localized to the gastric mucosa, pancreas, hypothalamus, kidneys, and pituitary gland.[16] When ghrelin was administered intravenously to healthy volunteers, the amount of food they consumed from a free-choice buffet was significantly greater compared with volunteers who received intravenous saline.[17] Ghrelin antagonists may treat excessive food intake, while ghrelin agonists may treat anorexia associated with cancer.[15,17]

Research on the hormone leptin has been more extensive because its discovery predates that of ghrelin. Leptin is produced by adipocytes and exerts its effects by acting on the hypothalamus to inhibit food intake and weight gain.[18,19] Elevated leptin levels stimulate lipolysis and a higher level of energy expenditure.[20] Conversely, the absence of leptin results in extreme obesity in humans and rodents.[21] Systemic leptin administration reduced food intake and body weight in *ob/ob* mice.[22,23] Further, a study presented by Heymsfield et al.[20] demonstrated that subcutaneous administration of leptin resulted in significant weight loss in obese humans.

Adiponectin, ghrelin, and leptin levels are also affected by weight changes and gastric bypass surgery.[24–26] Recent studies have demonstrated that ghrelin and adiponectin levels increase while leptin levels decrease after Roux-en-Y gastric bypass surgery.[26,27] Decreasing peripheral fat stores through liposuction may also affect the action of adiponectin, ghrelin, and leptin. One study reported a significant decrease in leptin levels 1 week after liposuction, but at 6 weeks the decrease was not significant.[27] Liposuction may alter other hormones as well.

Studies investigating improvement of health after liposuction in adults have demonstrated conflicting results. Giese et al.[28] first demonstrated systemic health benefits from high-volume liposuction, such as decreased weight, body fat mass, systolic blood pressure, and fasting insulin levels. A study by Gonzalez-Ortiz et al.[29] showed decreased plasma glucose levels and improved insulin sensitivity within a month of liposuction. Giugliano et al.[30] demonstrated improvement in metabolic factors and inflammatory mediators affecting cardiac health 6 months after liposuction, whereas Klein et al.[31] failed to demonstrate an improvement in these factors. Klein et al. did show elevation in leptin levels 10 to 12 weeks after liposuction.[31] Further animal and human studies are currently being performed to investigate the positive effects of fat loss through liposuction.

We chose to study the levels of ghrelin, adiponectin, and leptin after liposuction in obese male Zucker rats. In addition, we altered the fat and carbohydrate content of the postoperative diets of the rats to determine whether diet affects hormone levels after liposuction.

MATERIALS AND METHODS

Thirty-five male, 8- to 10-week-old obese Zucker rats were obtained from a commercial breeder (Harlan, Indianapolis, Ind.). The rats were housed two per cage and kept at a constant temperature and humidity in a room with an artificial 12-hour-light, 12-hour-dark cycle. The rats were fed a standard commercial laboratory chow (Teklad, Inc., Monmouth, Ill.) and drank unaltered tap water, both ad libitum. All animals had at least a 1-week period of acclimatization before they were used in experiments. The Institutional Animal Care and Use Committee of the Sinai Hospital of Baltimore, under established guidelines for the humane use and care of laboratory animals published by the United States Department of Agriculture, approved all protocols.

The rats were divided into three experimental groups and one control, unoperated group. Group I ($n = 10$) was fed a low-fat/low-carbohydrate diet (Bioserv, Frenchtown, N.J.); group II ($n = 10$) was fed a regular chow diet; and group III ($n = 10$) was fed a high-fat/high-carbohydrate diet. Diets were started on day 0 after liposuction was performed. There were five rats in the baseline control group.

On day 0, animals were anesthetized with intraperitoneal pentobarbital (50 mg/kg) and their abdomens were shaved, prepared with iodine surgical solution, and draped with sterile drapes. The midline was marked. A no. 15 scalpel blade was used to make a stab incision in the left lower quadrant of the abdomen. Ten milliliters of wetting solution (30 cc of 1% lidocaine plus 1 cc of 1:1000 epinephrine in 1 liter of lactated Ringer's solution at room temperature) was infiltrated subcutaneously in the left side of the abdomen. Subcutaneous liposuction was then performed on the left side of the abdomen using syringe liposuction

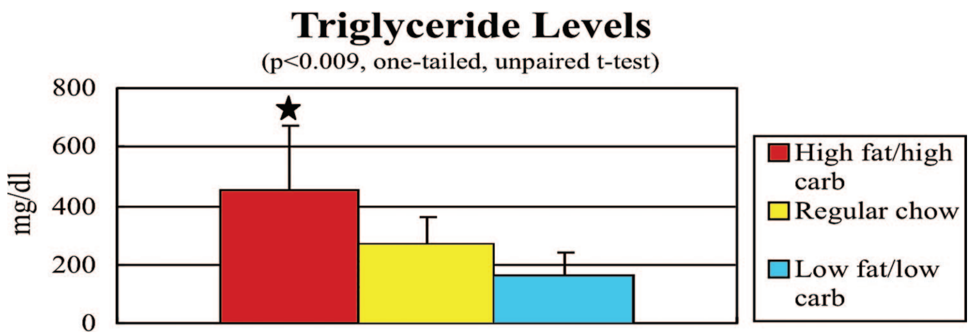

Fig. 1. Triglyceride levels, day 42 (high-fat/high-carbohydrate group, $n = 10$; regular chow group, $n = 9$; low-fat/low-carbohydrate group, $n = 10$). The *star* signifies statistical significance for the triglyceride level in the high-fat/high-carbohydrate group versus the other two groups ($p < 0.009$ by one-tailed, unpaired *t* test). The *T-bar* above the rectangle signifies standard deviation.

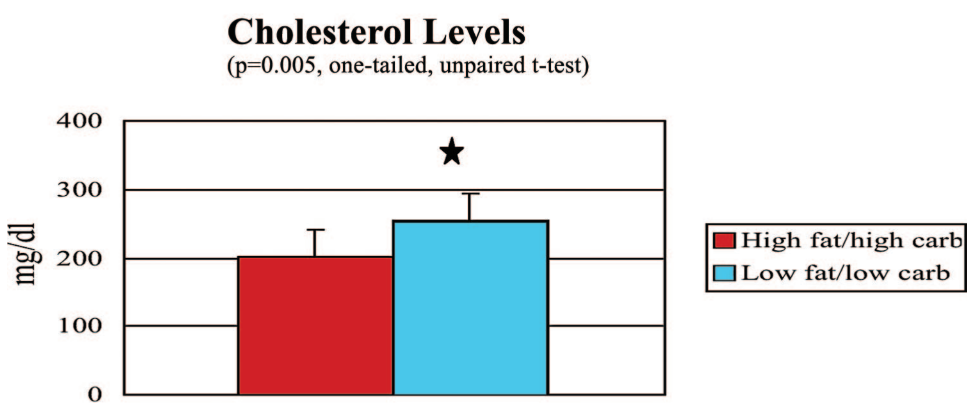

Fig. 2. Cholesterol levels, day 42 (high-fat/high-carbohydrate group, $n = 10$; low-fat/low-carbohydrate group, $n = 10$). The *star* signifies statistical significance for the cholesterol level in the low-fat/low-carbohydrate group versus the high-fat/high-carbohydrate group ($p = 0.005$, by one-tailed, unpaired *t* test with Bonferroni correction for multiple comparisons). The *T-bar* above the rectangle signifies standard deviation.

with vacuum provided by a Johnnie lock on a Toomey syringe (Mentor, Santa Barbara, Calif.). The total and percentage fatty aspirate were recorded. The wounds were closed with a single 5-0 nylon simple suture that was removed at 2 weeks. For 6 weeks, the study rats were fed their respective experimental diets.

Animals were euthanized on day 42 using 200 mg/kg intraperitoneal sodium pentobarbital. Blood samples were collected for analysis of adiponectin, ghrelin, and leptin levels, as well as triglyceride and cholesterol levels. To determine baseline hormone values, the five control rats were euthanized on day 0 using 200 mg/kg intraperitoneal sodium pentobarbital, and blood samples were collected. Blood samples were immediately placed on ice and transferred to a −70° freezer for later analysis.

Statistical analysis was performed using unpaired one-tailed *t* tests using Intercooled Stata 6.0 (Stata, College Station, Texas). The Bonferroni method was used to control for multiple comparisons.

RESULTS

One rat from the regular diet experimental group died before the 42-day period. The average total liposuction aspirate and average percentage of fat/aspirate in each group were 10.8 cc and 19.4 percent in the low-fat/low-carbohydrate group, 11.4 cc and 22.3 percent in the regular chow group, and 12.4 cc and 24.7 percent in the high-fat/high-carbohydrate group, respectively. These differences were not statistically significant, indicating that essentially similar volumes were aspirated from all groups (two-tailed unpaired *t* test).

Effect of Diet

The triglyceride level was significantly higher in the high-fat/high-carbohydrate group com-

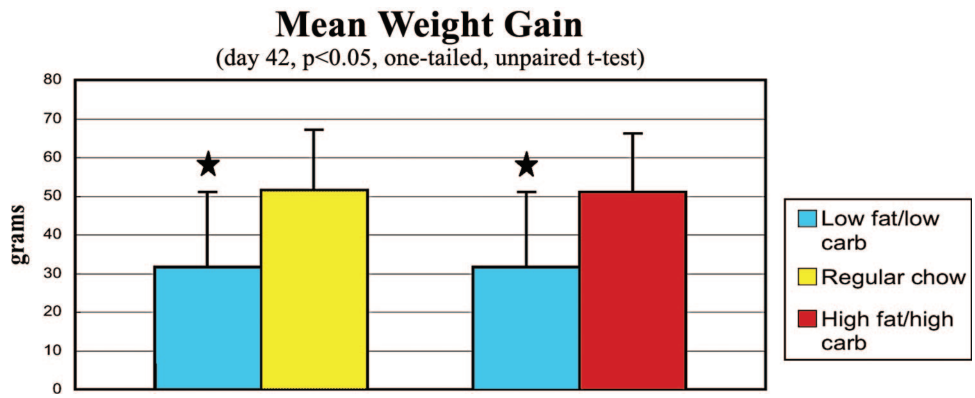

Fig. 3. Mean weight gain at day 42 (high-fat/high-carbohydrate group, $n = 10$; regular chow group, $n = 9$; low-fat/low-carbohydrate group, $n = 10$). The *star* signifies statistical significance for the weight gain in the low-fat/low-carbohydrate group versus the high-fat/high-carbohydrate group ($p < 0.004$) and the low-fat/low-carbohydrate group versus the regular diet group ($p < 0.0004$), by one-tailed, unpaired *t* test. The *T-bar* above the rectangle signifies standard deviation.

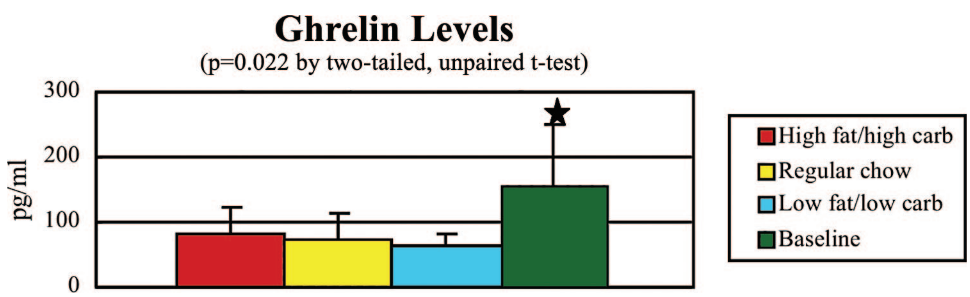

Fig. 4. Ghrelin levels, day 42 (high-fat/high-carbohydrate group, $n = 10$; regular chow group, $n = 9$; low-fat/low-carbohydrate group, $n = 10$; baseline group, $n = 5$). The *star* signifies statistical significance for the baseline level versus the other three groups ($p = 0.022$ by two-tailed, unpaired *t* test with Bonferroni correction for multiple comparisons). The *T-bar* above the rectangle signifies standard deviation.

pared with the regular chow and low-fat/low-carbohydrate groups (456 ± 204 versus 267 ± 94.3 versus 165 ± 76.1 mg/dl, $p < 0.009$ by one-tailed, unpaired *t* test) (Fig. 1). The cholesterol levels demonstrated a decreasing trend from the low-fat/low-carbohydrate group to the high-fat/high-carbohydrate group. They were significantly lower in the high-fat/high-carbohydrate group compared with the low-fat/low-carbohydrate group (202 ± 40 versus 254 ± 40 mg/dl, $p = 0.005$, by one-tailed, unpaired *t* test) (Fig. 2).

The mean weight gain demonstrated an increasing trend among the groups (31.7 g versus 51.6 g versus 51.1 g), with significance when comparing the low-fat group to the regular diet group ($p < 0.004$, unpaired *t* test) and the low-fat group to the high-fat group ($p < 0.0004$, one-tailed, unpaired *t* test) (Fig. 3).

Effect of Liposuction

Baseline ghrelin levels were significantly higher when compared with groups that underwent liposuction (low-fat/low-carbohydrate group, 61.6 ± 22.2; regular chow group, 70.5 ± 40.9; high-fat/high-carbohydrate group, 81.7 ± 39.5; baseline group, 153 ± 98.3 pg/ml; $p = 0.022$ by two-tailed, unpaired *t* test Bonferroni correction for multiple comparisons) (Fig. 4).

Postoperative liposuction leptin levels demonstrated an increasing trend from baseline (low-fat/low-carbohydrate group, 111 ± 35.8 pg/ml; regular chow group, 126 ± 23.9 pg/ml; high-fat/high-carbohydrate group, 153 ± 36.3 pg/ml; baseline group, 104 ± 23.1 pg/ml; $p > 0.05$ by two-tailed, unpaired *t* test) (Fig. 5).

Adiponectin levels did not demonstrate any significant change with liposuction or diet by two-

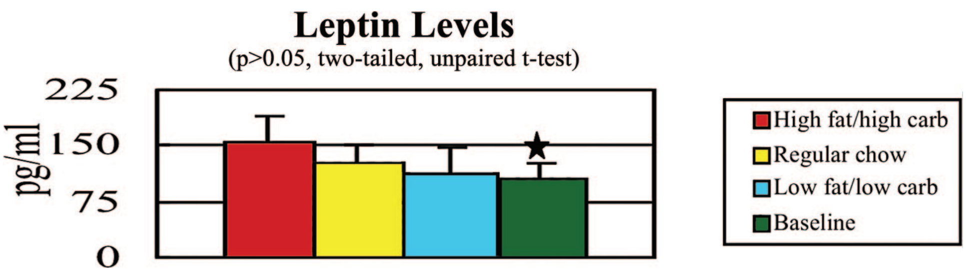

Fig. 5. Leptin levels, day 42 (high-fat/high-carbohydrate group, $n = 10$; regular chow group, $n = 9$; low-fat/low-carbohydrate group, $n = 10$; baseline group, $n = 5$). The *star* signifies statistical significance for the baseline level versus the other three groups by two-tailed, unpaired *t* test. The *T-bar* above the rectangle signifies standard deviation.

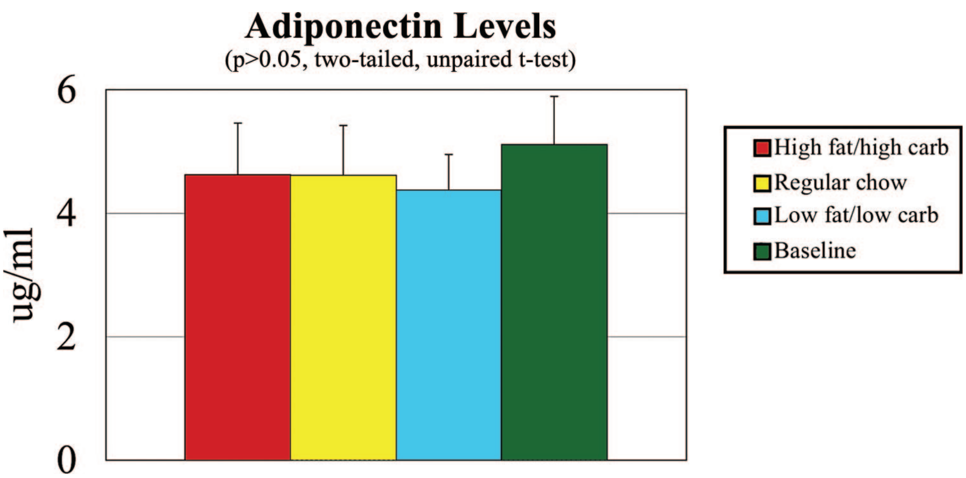

Fig. 6. Adiponectin levels, day 42 (high-fat/high-carbohydrate group, $n = 10$; regular chow group, $n = 9$; low-fat/low-carbohydrate group, $n = 10$; baseline group, $n = 5$). The *T-bar* above the rectangle signifies standard deviation. There was no statistically significant difference between groups by two-tailed, unpaired *t* test.

tailed, unpaired *t* test with Bonferroni correction for multiple comparisons (Fig. 6).

DISCUSSION

When Dr. Yves-Gerard Illouz introduced liposuction in 1974, he could not have predicted that it might become a therapy to treat obesity, diabetes, and cardiac disease.[32] Giese et al.[28] presented one of the initial studies demonstrating improved cardiac profiles in patients undergoing high-volume liposuction. The results of the study presented here may support these beneficial effects.

The fact that the triglyceride levels were significantly higher and the cholesterol levels were significantly lower in the high-fat/high-cholesterol group indicates how the Zucker rat metabolizes excess fat in the diet. This concurs with a prior study demonstrating that male obese Zucker rats do not overproduce cholesterol.[33] Triglycerides are the dominant form of lipid expressed in the Zucker rat following a high-fat/high-carbohydrate diet.

Ghrelin administration to humans has been shown to increase hunger and food intake.[17] Patients who sustain massive weight loss after gastric bypass surgery have ghrelin levels lower than those of matched obese or lean controls.[34] After liposuction in the Zucker rats, all groups demonstrated a decrease in ghrelin levels. Therefore, liposuction may promote further weight loss by decreasing appetite and food intake via lower circulating ghrelin levels. Ghrelin levels were not significantly affected by a difference in diet.

After liposuction, leptin levels increased in all groups, possibly because of liberation of leptin from the subcutaneous fat stores. Interestingly, studies have demonstrated that leptin administered to leptin-deficient mice reverses obesity or causes leanness in normal mice.[35,36] Liposuction leading to elevated leptin levels may therefore provide a protective effect beyond thinning subcutaneous fat layers. These data contrast with the previously published liposuction study in humans that demonstrated an acute decrease in leptin 1 week after liposuction. In the present study, leptin levels also increased as the amount of fat and carbohydrate in the diet was augmented, possibly indicating a feedback mechanism to the brain to regulate fat intake.

Adiponectin was not significantly affected by either diet or liposuction. This is seemingly unusual, since the other fat hormones did appear to change in response to liposuction and/or diet. The literature supports the lack of effect on adiponectin. Despite alterations in adiponectin levels with massive weight loss, Ryan et al. found no effect on serum adiponectin levels with moderate weight loss in obese women.[37,38] A study investigating postprandial adiponectin levels found no alteration in response to a fat meal.[39] Further, a study utilizing Zucker rats reported the significance of studying visceral fat over subcutaneous fat with regard to adiponectin.[40] Furthermore, the complexity of hormonal interactions coupled with physiologic changes makes it difficult to isolate effects on a single hormone, particularly since the effects may be secondary to regulatory mechanisms and not direct.

This study is preliminary and only provides a glimpse into the realm of liposuction and its effect on obesity-related hormones. Human studies are required to delineate hormone levels before and after liposuction, and peripheral administration and/or blockade of specific hormones may augment the fat-reducing effects of liposuction. This study opens the door for more research defining the possible therapeutic role of liposuction in the treatment of obesity.

CONCLUSIONS

We have shown decreased ghrelin and increased leptin levels after liposuction in obese Zucker rats. Adiponectin levels were not affected. Liposuction may prove to offer patients medically therapeutic benefits through hormonal alterations. Although a high-fat/high-carbohydrate diet elevated circulating triglyceride levels, it did not adversely affect fat-related hormone levels, possibly through a protective effect that liposuction provides. Lastly, we have shown that diet plays an important role in weight gain after liposuction. Animals consuming a diet low in fat and cholesterol had lower weight gain compared with those animals consuming a diet of regular chow and those consuming a diet high in fat and cholesterol.

Michele A. Shermak, M.D.
Division of Plastic Surgery
Johns Hopkins Bayview Medical Center
4940 Eastern Avenue, Suite A518
Baltimore, Md. 21224
masherma@jhmi.edu

REFERENCES

1. DeJong, G., Sheppard, L., Lieber, M., and Chenoweth, D. The cost of being couch potato. *Mich. Health Hosp.* 39: 24, 2003.
2. American Obesity Association. Web site available at http://www.obesity.org. Accessed August 2003.
3. Flegal, K. M., Carroll, M. D., Ogden, C. L., and Johnson, C. L. Prevalence and trends in obesity among US adults, 1999-2000. *J.A.M.A.* 288: 1723, 2002.
4. Spiegelman, B. M., and Flier, J. S. Obesity and the regulation of energy balance. *Cell* 104: 531, 2001.
5. Kuczmarski, R. J., Flegal, K. M., Campbell, S. M., and Johnson, C. L. Increasing prevalence of overweight among US adults: The National Health and Nutrition Examination Surveys, 1960 to 1991. *J.A.M.A.* 272: 205, 1994.
6. Report of a WHO Consultation on Obesity. Geneva, Switzerland: World Health Organization, 1997.
7. National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The evidence report. *Obes. Res.* 6: 51S, 1998.
8. Allison, D. B., Fontaine, K. R., Manson, J. E., et al. Annual deaths attributable to obesity in the United States. *J.A.M.A.* 282: 1530, 1999.
9. Fontaine, K. R., Redden, D. T., Wang, C., Westfall, A. O., and Allison, D. B. Years of life lost due to obesity. *J.A.M.A.* 289: 187, 2003.
10. Kuhajda, F. P. Fatty-acid synthase and human cancer: New perspectives on its role in tumor biology. *Nutrition* 16: 202, 2000.
11. Nilsson, M., Johnsen, R., Ye, W., et al. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *J.A.M.A.* 290: 66, 2003.
12. Fortuno, A., Rodriquez, A., Gomez-Ambrosi, J., et al. Adipose tissue as an endocrine organ: Role of leptin and adiponectin in the pathogenesis of cardiovascular diseases. *J. Physiol. Biochem.* 59: 51, 2003.
13. Kern, P., Di, G. G., Lu, T., Rassouli, N., and Ranganathan, G. Adiponectin expression from human adipose tissue: Relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. *Diabetes* 52: 1779, 2003.
14. Vasseur, F., Lepretre, F., Lacquemant, C., and Froguel, P. The genetics of adiponectin. *Curr. Diab. Rep.* 3: 151, 2003.
15. Espelund, U., Hansen, T., Orskov, H., and Frystyk, J. Assessment of ghrelin. *A.P.M.I.S. Suppl.* 109: 140, 2003.
16. Holdstock, C., Engstrom, B., Ohrvall, M., Lind, L., Sundbom, M., and Karlsson, F. Ghrelin and adipose tissue regulatory peptides: Effect of gastric bypass surgery in obese humans. *J. Clin. Endocrinol. Metab.* 88: 3177, 2003.
17. Wren, A., Seal, L., Cohen, M., et al. Ghrelin enhances appetite and increases food intake in humans. *J. Clin. Endocrinol. Metab.* 86: 5992, 2001.
18. Halle, M., Berg, A., Garwers, U., et al. Concurrent reductions of serum leptin and lipids during weight loss in obese men

with type 2 diabetes. *Am. J. Physiol. Endocrinol. Metab.* 277: E277, 1999.
19. Schwartz, M., Woods, S., Porte, D., Jr., Seeley, R., and Baskin, D. Central nervous system control of food intake. *Nature* 404: 661, 2000.
20. Heymsfield, S., Greenberg, A., Fujioka, K., et al. Recombinant leptin for weight loss in obese and lean adults: A randomized, controlled, dose-escalation trial. *J.A.M.A.* 282: 1568, 1999.
21. Montague, C., Farooqi, I., Whitehead, J., Soos, M., Rau, H., and Wareham, N. Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 387: 903, 1997.
22. Cusin, I., Rohner-Jeanrenaud, F., Stricker-Krongrad, A., and Jeanrenaud, B. The weight-reducing effect of an intracerebroventricular bolus injection of leptin in genetically obese fa/fa rats: Reduced sensitivity compared with lean animals. *Diabetes* 45: 1446, 1996.
23. Halaas, J., Boozer, C., Blair-West, J., Fidahusein, N., Denton, D., and Friedman, J. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proc. Natl. Acad. Sci. U.S.A.* 94: 8878, 1997.
24. Halaas, J. L., Gajiwala, K. S., Maffei, M., et al. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* 269: 543, 1995.
25. Holdstock, C., Engstrom, B. E., Ohrvall, M., et al. Ghrelin and adipose tissue regulatory peptides: Effect of gastric bypass surgery in obese humans. *J. Clin. Endocrinol. Metabol.* 88: 3177, 2003.
26. Faraj, M., Havel, P., Phelis, S., Blank, D., Sniderman, A., and Cianflone, K. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. *J. Clin. Endocrinol. Metab.* 88: 1594, 2003.
27. Talisman, R., Belinson, N., Modan-Moses, D., et al. The effect of reduction of the peripheral fat content by liposuction-assisted lipectomy (SAL) on serum leptin levels in the postoperative period: A prospective study. *Aesthetic Plast. Surg.* 25: 262, 2001.
28. Giese, S., Bulan, E., Commons, G., Spear, S., and Yanovski, J. Improvements in cardiovascular risk profile with large-volume liposuction: A pilot study. *Plast. Reconstr. Surg.* 108: 510, 2001.
29. Gonzalez-Ortiz, M., Robles-Cervantes, J. A., Cardenas-Camarena, L., et al. The effects of surgically removing subcutaneous fat on the metabolic profile and insulin sensitivity in obese women after large-volume liposuction treatment. *Horm. Metab. Res.* 34: 446, 2002.
30. Giugliano, G., Nicoletti, G., Grella, E., et al. Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women. *Br. J. Plast. Surg.* 57: 190, 2004.
31. Klein, S., Fontana, L., Young, V. L., et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N. Engl. J. Med.* 350: 2549, 2004.
32. Illouz, Y. History and current concepts of lipoplasty. *Clin. Plast. Surg.* 23: 721, 1996.
33. McNamara, D. J. Cholesterol homeostasis in lean and obese male Zucker rats. *Metabolism* 34: 130, 1985.
34. Cummings, D. E., and Shannon, M. H. Ghrelin and gastric bypass: Is there a hormonal contribution to surgical weight loss? *J. Clin. Endocrinol. Metabol.* 88: 2999, 2003.
35. Friedman, J. M., and Halaas, J. L. Leptin and the regulation of body weight in mammals. *Nature* 395: 763, 1998.
36. Halaas, J. L., Gajiwala, K. S., Maffei, M., et al. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* 269: 543, 1995.
37. Asayama, K. A., Hayashibe, H., Dobashi, K., et al. Decrease in serum adiponectin level due to obesity and visceral fat accumulation in children. *Obes. Res.* 11: 1072, 2003.
38. Ryan, A. S., Nicklas, B. J., Berman, D. M., and Elahi, D. Adiponectin levels do not change with moderate dietary induced weight loss and exercise in obese postmenopausal women. *Int. J. Obes.* 27: 1066, 2003.
39. Peake, P. W., Kriketos, A. D., Denyer, G. S., et al. The postprandial response of adiponectin to a high-fat meal in normal and insulin-resistant subjects. *Int. J. Obes. Relat. Metab. Disord.* 27: 657, 2003.
40. Altomonte, J., Harbaran, S., Richter, A., and Dong, H. Fat depot-specific expression of adiponectin is impaired in Zucker fatty rats. *Metabolism* 52: 958, 2003.