

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JUNE 17, 2004

VOL. 350 NO. 25

Absence of an Effect of Liposuction on Insulin Action and Risk Factors for Coronary Heart Disease

Samuel Klein, M.D., Luigi Fontana, M.D., Ph.D., V. Leroy Young, M.D., Andrew R. Coggan, Ph.D., Charles Kilo, M.D., Bruce W. Patterson, Ph.D., and B. Selma Mohammed, M.D., Ph.D.

ABSTRACT

BACKGROUND

Liposuction has been proposed as a potential treatment for the metabolic complications of obesity. We evaluated the effect of large-volume abdominal liposuction on metabolic risk factors for coronary heart disease in women with abdominal obesity.

METHODS

We evaluated the insulin sensitivity of liver, skeletal muscle, and adipose tissue (with a euglycemic–hyperinsulinemic clamp procedure and isotope-tracer infusions) as well as levels of inflammatory mediators and other risk factors for coronary heart disease in 15 obese women before and 10 to 12 weeks after abdominal liposuction. Eight of the women had normal glucose tolerance (mean [\pm SD] body-mass index, 35.1 \pm 2.4), and seven had type 2 diabetes (body-mass index, 39.9 \pm 5.6).

RESULTS

Liposuction decreased the volume of subcutaneous abdominal adipose tissue by 44 percent in the subjects with normal glucose tolerance and 28 percent in those with diabetes; those with normal oral glucose tolerance lost 9.1 \pm 3.7 kg of fat (18 \pm 3 percent decrease in total fat, $P=0.002$), and those with type 2 diabetes lost 10.5 \pm 3.3 kg of fat (19 \pm 2 percent decrease in total fat, $P<0.001$). Liposuction did not significantly alter the insulin sensitivity of muscle, liver, or adipose tissue (assessed by the stimulation of glucose disposal, the suppression of glucose production, and the suppression of lipolysis, respectively); did not significantly alter plasma concentrations of C-reactive protein, interleukin-6, tumor necrosis factor α , and adiponectin; and did not significantly affect other risk factors for coronary heart disease (blood pressure and plasma glucose, insulin, and lipid concentrations) in either group.

CONCLUSIONS

Abdominal liposuction does not significantly improve obesity-associated metabolic abnormalities. Decreasing adipose tissue mass alone will not achieve the metabolic benefits of weight loss.

From the Center for Human Nutrition, Washington University School of Medicine, St. Louis (S.K., L.F., V.L.Y., A.R.C., C.K., B.W.P., B.S.M.); and the Division of Food Science, Human Nutrition and Health, Istituto Superiore di Sanità Rome, Rome (L.F.). Address reprint requests to Dr. Klein at Washington University School of Medicine, 660 South Euclid Ave., Campus Box 8031, St. Louis, MO 63110.

N Engl J Med 2004;350:2549-57.

Copyright © 2004 Massachusetts Medical Society.

ABDOMINAL OBESITY, MANIFESTED BY increased waist circumference, increased abdominal subcutaneous fat, and increased visceral fat, is associated with insulin resistance and other metabolic risk factors for coronary heart disease.¹ Although both the abdominal subcutaneous fat mass and the visceral fat mass are associated with insulin resistance,² it is not known whether one or both of these fat depots are actually involved in the pathogenesis of insulin resistance or whether they are simply associated with the metabolic complications of obesity.

Diet-induced weight loss improves the metabolic complications of abdominal obesity. However, successful long-term weight management is difficult to achieve, and the majority of obese persons who lose weight by implementing lifestyle changes regain their lost weight over time.³ Frustration with the efficacy of current obesity therapies has led to increased interest in alternative approaches. Recently, it has been suggested that liposuction, which can remove large amounts of body fat, is a potential treatment for the metabolic complications of obesity.⁴⁻⁷

Liposuction, also known as lipoplasty or suction-assisted lipectomy, is the most common aesthetic surgical procedure performed in the United States; nearly 400,000 procedures are performed annually.⁸ Recent advances in liposuction techniques now make it possible to remove considerable amounts of subcutaneous adipose tissue.⁹ Therefore, abdominal liposuction provides a unique opportunity to evaluate the importance of subcutaneous abdominal fat in the pathogenesis of insulin resistance and in the risk of coronary heart disease in persons with abdominal obesity. However, the metabolic effects of liposuction are unclear because the results of studies have varied.^{5-7,10,11} The interpretation of data from such studies is confounded by lifestyle and weight changes that occurred among the subjects after liposuction was performed, by variations in the volume of adipose tissue removed and the site of its removal, by differences in the methods used to assess insulin sensitivity, and by differences in the subjects' baseline weight and insulin sensitivity.

The purpose of the present study was to determine the effect of large-volume abdominal liposuction on insulin sensitivity in liver, skeletal muscle, and adipose tissue (evaluated with the use of a two-stage euglycemic-hyperinsulinemic clamp procedure, in conjunction with stable isotope-tracer infusions) and on risk factors for coronary heart disease

(waist circumference, blood pressure, plasma lipid concentrations, and serum markers of inflammation) in women with abdominal obesity. Obese women with normal glucose tolerance and those with type 2 diabetes were studied to assess the potential beneficial effects of liposuction in persons with moderate or severe insulin resistance.

METHODS

SUBJECTS

We studied eight women with abdominal obesity (waist circumference, more than 100 cm) who had normal oral glucose tolerance but moderate insulin resistance (mean [\pm SD] age, 42 \pm 3 years) and seven women with abdominal obesity who had type 2 diabetes and more severe insulin resistance (age, 52 \pm 3 years). The women with type 2 diabetes were being treated with a combination of two or three oral hypoglycemic medications (glipizide, glyburide, glimepiride, rosiglitazone, pioglitazone, or metformin). They were consecutive eligible patients who were scheduled to undergo large-volume liposuction performed by one of the authors and were enrolled between November 2001 and March 2003. No evidence of other serious illnesses or organ dysfunction was found after the subjects had completed a comprehensive medical evaluation, which included a history and physical examination, electrocardiography, standard blood and urine tests, and a two-hour oral glucose-tolerance test. All the subjects had had a stable weight (with fluctuations of not more than 2 percent of the body weight) for at least two months and had been sedentary (exercising for less than one hour per week) for at least six months before entering the study. Each subject provided written informed consent before participating, and the study was approved by the human studies committee of Washington University School of Medicine, St. Louis.

STUDY DESIGN

Assessments of Body Composition

Each subject's body composition was assessed within nine days before liposuction. Total body fat and fat-free mass were determined by dual-energy x-ray absorptiometry (Hologic QDR 1000/w). Abdominal and thigh fat masses were quantified by means of magnetic resonance imaging (Siemens). Eight 10-mm-thick slice images were obtained both at the L4-L5 interspace and at the superior border of the medial condyle of the tibia and were analyzed

for subcutaneous and intracompartmental (abdomen or muscle) fat content.

Euglycemic–Hyperinsulinemic Clamp Protocol

The subjects were admitted to the General Clinical Research Center (Washington University School of Medicine) and consumed a standard meal (55 percent carbohydrate, 30 percent fat, and 15 percent protein) containing 16 kcal per kilogram of fat-free mass at 7 p.m. At 8 p.m., they consumed a 240-kcal liquid snack (Ensure, Ross Laboratories). The last dose of hypoglycemic medication was taken on the day of admission. At 5 a.m. the next morning, after the subjects had fasted overnight, catheters were inserted into a radial artery for blood sampling and into an antecubital vein for the infusion of insulin, dextrose, and tracers. At 7 a.m., a primed (priming dose, 4.1 mg per kilogram [22.5 μ mol per kilogram]), constant infusion of [6,6- 2 H $_2$]glucose (0.46 mg per minute per kilogram [0.25 μ mol per minute per kilogram]) was started, followed at 9 a.m. by a primed (priming dose, 116 μ g per kilogram [1.2 μ mol per kilogram]), constant infusion of [1,1,2,3,3- 2 H $_5$]glycerol (7.8 μ g per minute per kilogram [0.08 μ mol per minute per kilogram]) and a constant infusion of [2,2- 2 H $_2$]palmitate (9.0 μ g per minute per kilogram [0.035 μ mol per minute per kilogram]).

After infusion of the tracer for 3.5 hours (the basal period), a two-stage euglycemic–hyperinsulinemic clamp protocol was initiated and continued for 6 hours. Euglycemia (a glucose level of approximately 100 mg per deciliter [5.6 mmol per liter]) was maintained by variable-rate infusion of 20 percent dextrose containing approximately 2.5 percent [6,6- 2 H $_2$]glucose. During stage 1 of the clamp protocol (from hour 3.5 to hour 6.5 of the tracer-infusion study), insulin was infused at a rate of 20 mU per square meter of body-surface area per minute after initiation by a two-step priming dose of insulin for 10 minutes (80 mU per square meter per minute for 5 minutes, followed by 40 mU per square meter per minute for 5 minutes). During stage 2 of the clamp protocol (hour 6.5 to hour 9.5 of the tracer-infusion study), insulin was infused at a rate of 50 mU per square meter per minute after initiation by a two-step priming dose of insulin for 10 minutes (200 mU per square meter per minute for 5 minutes, followed by 100 mU per square meter per minute for 5 minutes).

These insulin infusion rates result in plasma insulin concentrations that provide an optimal range

for evaluating the effect of insulin on glucose production and lipolysis (stage 1) and on glucose disposal (stage 2). The rates of tracer infusions were decreased during each stage of the clamp protocol to account for the expected changes in endogenous substrate metabolism. Blood samples were obtained before the beginning of the tracer infusion to determine baseline plasma concentrations of C-reactive protein, cytokines, lipids, substrates, and hormones and to determine background substrate tracer-to-tracee ratios. Blood was collected every 10 minutes during the last 30 minutes of the basal period and during the last 30 minutes of each stage of the euglycemic–hyperinsulinemic clamp procedure to determine plasma substrate and insulin concentrations and substrate tracer-to-tracee ratios (i.e., the ratios of labeled to unlabeled substrate in plasma). Plasma was separated by centrifugation within 30 minutes after collection and stored at -70° C until final analyses were performed.

Liposuction

Approximately one week after completing the euglycemic–hyperinsulinemic clamp procedure, each subject underwent large-volume tumescent liposuction, defined as the removal of more than 4 liters of aspirate.¹² This procedure involves subcutaneous injection of a large volume of Ringer's lactate containing dilute epinephrine (1:1,000,000) to induce vasoconstriction and thus to minimize bleeding. All liposuction procedures were performed by one of the authors, who primarily removed superficial and deep subcutaneous abdominal fat. In addition, smaller amounts of fat were removed from the arms, flanks, hips, or thighs in five subjects without diabetes and in four subjects with diabetes. A total of 16 \pm 1 liters (12 \pm 1 liters from the upper body and 4 \pm 2 liters from the lower body) of Ringer's lactate plus epinephrine-infiltrated adipose tissue was aspirated from the subjects with normal oral glucose tolerance and a total of 17 \pm 2 liters (16 \pm 2 liters from the upper body and 1 \pm 1 liters from the lower body) was aspirated from the subjects with type 2 diabetes.

Evaluation after Liposuction

Subjects were instructed to resume their normal lifestyle after the initial recovery period and to weigh themselves weekly at home. Each subject was contacted by one of the investigators at least once every week by phone to review her medical condition and to reinforce the importance of maintaining her usual food intake and physical activity and to main-

tain a stable body weight. No serious complications occurred in any subject, and all were able to return to their usual lifestyle within 10 days after liposuction. For each of the seven subjects with type 2 diabetes, hypoglycemic medications were regulated by the subject's physician. In six of them, the medications were not changed after the clamp procedure; in one, rosiglitazone (4 mg per day) was stopped, and glipizide and metformin were continued.

All the studies performed before liposuction were repeated 10 to 12 weeks after liposuction. The 10-to-12-week delay was intended to eliminate the confounding effects of postsurgical inflammation on our study end points.

ANALYSES OF BLOOD SAMPLES

Plasma glucose concentrations were determined with use of a glucose analyzer (Yellow Springs Instruments), and plasma fatty acid concentrations were quantified by means of gas chromatography.¹³ Plasma insulin and leptin concentrations were measured by radioimmunoassay (Linco Research). Plasma lipid concentrations were determined enzymatically (Roche/Hitachi 747 Analyzer, Roche Diagnostics). Enzyme-linked immunosorbent assay kits were used to measure plasma C-reactive protein (American Laboratory Products), adiponectin (B-Bridge International), interleukin-6, and tumor necrosis factor α (Quantakine High Sensitive, R&D Systems). Plasma glucose, glycerol, and palmitate tracer-to-tracee ratios were determined with the use of gas chromatography–mass spectrometry.^{13,14}

CALCULATIONS

A physiologic and isotopic steady state was achieved during the last 30 minutes of the basal period and the insulin-infusion period, so the rates of appearance and disappearance of substrate were calculated as the tracer infusion rate divided by the tracer-to-tracee ratio.¹⁵ The rate of appearance of total free fatty acid was calculated by dividing the rate of appearance of palmitate by the percent contribution of palmitate to total plasma free fatty acids.

STATISTICAL ANALYSIS

The number of subjects to be enrolled was determined as the estimated number needed for the study to detect a statistically significant effect of liposuction on glucose kinetics with a power of at least 0.8, if the subjects had lost a similar amount of body fat by dieting. Data on subjects with diabetes and those

without diabetes were analyzed separately. A two-way analysis of variance (time by clamp stage) with repeated measures was used to compare the effects of liposuction on basal and insulin-mediated substrate metabolism. Changes in body composition and risk factors for coronary heart disease were assessed by means of Student's t-test for paired samples. All reported P values are two-sided, and a P value of 0.05 or less was considered to indicate statistical significance.

RESULTS

BODY COMPOSITION

Liposuction decreased body weight and body-mass index (the weight in kilograms divided by the square of the height in meters) because of a marked decrease in body fat (Table 1). Ten to 12 weeks after surgery, the mass of body fat had decreased by 9.1 ± 3.7 kg from baseline (18 ± 3 percent of the total fat mass, $P=0.002$) in the subjects with normal oral glucose tolerance and by 10.5 ± 3.3 kg (19 ± 2 percent of the total fat mass, $P<0.001$) in the subjects with type 2 diabetes. The decrease in measured fat mass was consistent with the amount of fat aspirated during liposuction; approximately 60 percent of the liposuction aspirate was composed of fat. The decrease in body fat was greater than the total decrease in body weight, however, because of abdominal-tissue edema, which often persists for months after liposuction.¹⁶ The measured truncal fat-free mass, which included tissue fluid, increased from 24.5 ± 2.7 kg to 27.4 ± 3.0 kg ($P<0.001$) in the two groups overall. Liposuction decreased the volume of subcutaneous abdominal adipose tissue by 44 percent in the subjects with normal glucose tolerance and 28 percent in those with diabetes, whereas the volumes of visceral adipose tissue and thigh adipose tissue did not change significantly (Fig. 1 and Table 1).

CIRCULATING INFLAMMATORY MEDIATORS AND OTHER RISK FACTORS FOR CORONARY HEART DISEASE

Liposuction caused a decrease in waist circumference in both groups, but it did not significantly alter other risk factors for coronary heart disease (Table 2). Liposuction also decreased plasma leptin concentrations in both groups, but it did not significantly alter the concentrations of other circulating cytokines or of C-reactive protein (Table 3).

Table 1. Effects of Liposuction on Body Composition in Obese Women with Normal Glucose Tolerance or Type 2 Diabetes.*

Variable	Normal Glucose Tolerance (N=8)				Type 2 Diabetes (N=7)			
	Before Liposuction	After Liposuction	Change (95% CI)	P Value	Before Liposuction	After Liposuction	Change (95% CI)	P Value
Body-mass index	35.1±2.4	32.7±2.7	-2.3 (-3.2 to -1.4)	0.002	39.9±5.6	36.0±5.1	-3.9 (-5.9 to -1.8)	0.01
Weight (kg)	100.0±9.5	93.7±10.6	-6.3 (-8.9 to -3.7)	0.002	106.5±14.7	98.6±13.0	-7.9 (-10.2 to -5.6)	<0.001
Fat mass (kg)	50.7±2.7	41.5±2.6	-9.1 (-12.9 to -5.4)	0.002	55.3±13.6	44.8±10.0	-10.5 (-13.8 to -7.2)	<0.001
Body fat (%)	50.5±3.6	44.2±4.7	-6.3 (-9.0 to -3.5)	0.003	51.7±6.7	45.0±5.2	-6.7 (-8.8 to -4.5)	<0.001
Adipose-tissue volume (cm ³)								
Subcutaneous abdominal	3414±818	1895±778	-1519 (-1977 to -1061)	<0.001	3803±661	2751±670	-1051 (-1688 to -415)	0.007
Visceral	1713±727	1673±853	-41 (-238 to +157)	0.70	2653±597	2425±643	-228 (-684 to +229)	0.30
Thigh	1732±608	1658±707	-73 (-190 to +44)	0.26	2038±547	1980±556	-58 (-131 to +16)	0.12

* Plus-minus values are means ±SD. Body-composition studies were performed within 9 days before liposuction and were repeated 10 to 12 weeks after liposuction. CI denotes confidence interval, minus signs decreases, and plus signs increases.

SUBSTRATE KINETICS AND INSULIN SENSITIVITY

In the subjects with normal glucose tolerance, plasma insulin concentrations after liposuction were similar to those before liposuction for both stages 1 and 2 of the clamp procedure (stage 1 and 2 values before liposuction, 44±7 and 90±12 μU per milliliter [264±42 and 540±72 pmol per liter], respectively; stage 1 and 2 values after liposuction, 42±5 and 89±6 μU per milliliter [252±30 and 534±48 pmol per liter], respectively); the same was true of the subjects with type 2 diabetes (stage 1 and 2 values before liposuction, 40±2 and 86±7 μU per milliliter [240±12 and 516±42 pmol per liter], respectively; stage 1 and 2 values after liposuction, 41±3 and 86±6 μU per milliliter [246±18 and 516±36 pmol per liter], respectively). Insulin infusion during stage 1 caused the expected decreases in the rates of appearance of glucose, glycerol, and free fatty acids, and insulin infusion during stage 2 caused the expected increase in the rate of disappearance of glucose both in subjects with normal glucose tolerance and in those with type 2 diabetes (Fig. 2 and 3). Rates of appearance of glucose, glycerol, and free fatty acid and the rate of disappearance of glucose during basal conditions and during each stage of the clamp procedure were not significantly different before and after liposuction in either group (Fig. 2 and 3).

DISCUSSION

In the present study, we evaluated the effects of large-volume liposuction on insulin sensitivity and

risk factors for coronary heart disease in women with abdominal obesity who had either moderate insulin resistance and normal glucose tolerance or more severe insulin resistance and type 2 diabetes. Weight stability was carefully maintained before and after liposuction to eliminate the confounding effects of changes in energy balance on the study end points. Our data show that the aspiration of large amounts of subcutaneous abdominal adipose tissue resulted in a considerable decrease in body weight, waist circumference, and plasma leptin concentrations but did not have a significant effect on

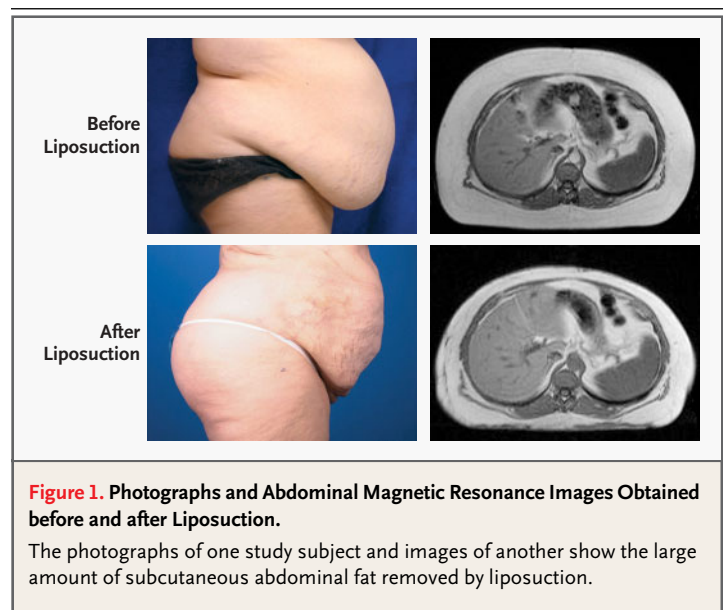


Table 2. Effects of Liposuction on Risk Factors for Coronary Heart Disease in Obese Women with Normal Glucose Tolerance or Type 2 Diabetes.*

Variable	Normal Glucose Tolerance (N=8)				Type 2 Diabetes (N=7)			
	Before Liposuction	After Liposuction	Change (95% CI)	P Value	Before Liposuction	After Liposuction	Change (95% CI)	P Value
Waist circumference (cm)	108±13	94±9	-14 (-21 to -6)	0.009	119±10	107±9	-12 (-20 to -5)	0.02
Blood pressure (mm Hg)								
Systolic	119±13	124±12	+5 (-5 to +15)	0.38	132±9	137±16	+5 (-6 to +17)	0.39
Diastolic	70±8	65±12	-5 (-13 to +2)	0.23	73±8	68±10	-5 (-13 to +3)	0.29
Plasma glucose (mg/dl)	89±4	90±6	+1 (-1 to +4)	0.33	121±39	123±41	+2 (-13 to +16)	0.84
Plasma insulin (μU/ml)	11±8	9±5	-2 (-4 to +2)	0.41	15±5	14±7	-1 (-5 to +2)	0.44
Cholesterol (mg/dl)								
Total	189±35	174±33	-15 (-33 to +3)	0.14	160±12	157±27	-3 (-20 to +15)	0.79
Low-density lipoprotein	113±26	110±32	-3 (-17 to +11)	0.67	82±17	80±28	-2 (-15 to +11)	0.78
High-density lipoprotein	45±12	41±13	-4 (-10 to 0)	0.11	44±8	43±7	-1 (-5 to +2)	0.37
Triglycerides (mg/dl)	151±79	121±58	-30 (-22 to +2)	0.11	162±49	173±65	+11 (-25 to +48)	0.56

* Plus-minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.0555. To convert the values for insulin to picomoles per liter, multiply by 6. To convert the values for cholesterol to millimoles per liter, multiply by 0.0259. To convert the values for triglycerides to millimoles per liter, multiply by 0.0113. The measurements were made within 9 days before liposuction and again 10 to 12 weeks after liposuction. CI denotes confidence interval, minus signs decreases, and plus signs increases.

Table 3. Effects of Liposuction on Mediators of Inflammation in Obese Women with Normal Glucose Tolerance or Type 2 Diabetes.*

Variable	Normal Glucose Tolerance (N=8)				Type 2 Diabetes (N=7)			
	Before Liposuction	After Liposuction	Change (95% CI)	P Value	Before Liposuction	After Liposuction	Change (95% CI)	P Value
Leptin (ng/ml)	31.7±12.0	23.5±5.4	-8.2 (-15.9 to -0.4)	0.05	35.7±13.5	30.2±12.6	-5.5 (-1.1 to -9.8)	0.05
Adiponectin (ng/ml)	5.0±2.2	4.5±2.2	-0.5 (-0.8 to ±0.1)	0.13	4.3±2.3	3.6±2.2	-0.7 (-1.5 to +0.1)	0.13
Tumor necrosis factor α (pg/ml)	3.5±5.8	2.8±3.3	-0.7 (-2.8 to +1.4)	0.54	7.6±8.3	7.7±7.8	+0.2 (-0.5 to +0.9)	0.60
Interleukin-6 (pg/ml) †	1.5±0.6	2.4±0.9	+0.9 (0 to +1.7)	0.10	3.8±3.8	3.2±2.5	-0.7 (-1.7 to +0.3)	0.24
C-reactive protein (μg/ml)	6.9±6.7	6.7±6.5	-0.2 (-1.1 to +0.8)	0.74	8.2±7.2	7.7±6.9	-0.5 (-1.3 to +0.4)	0.30

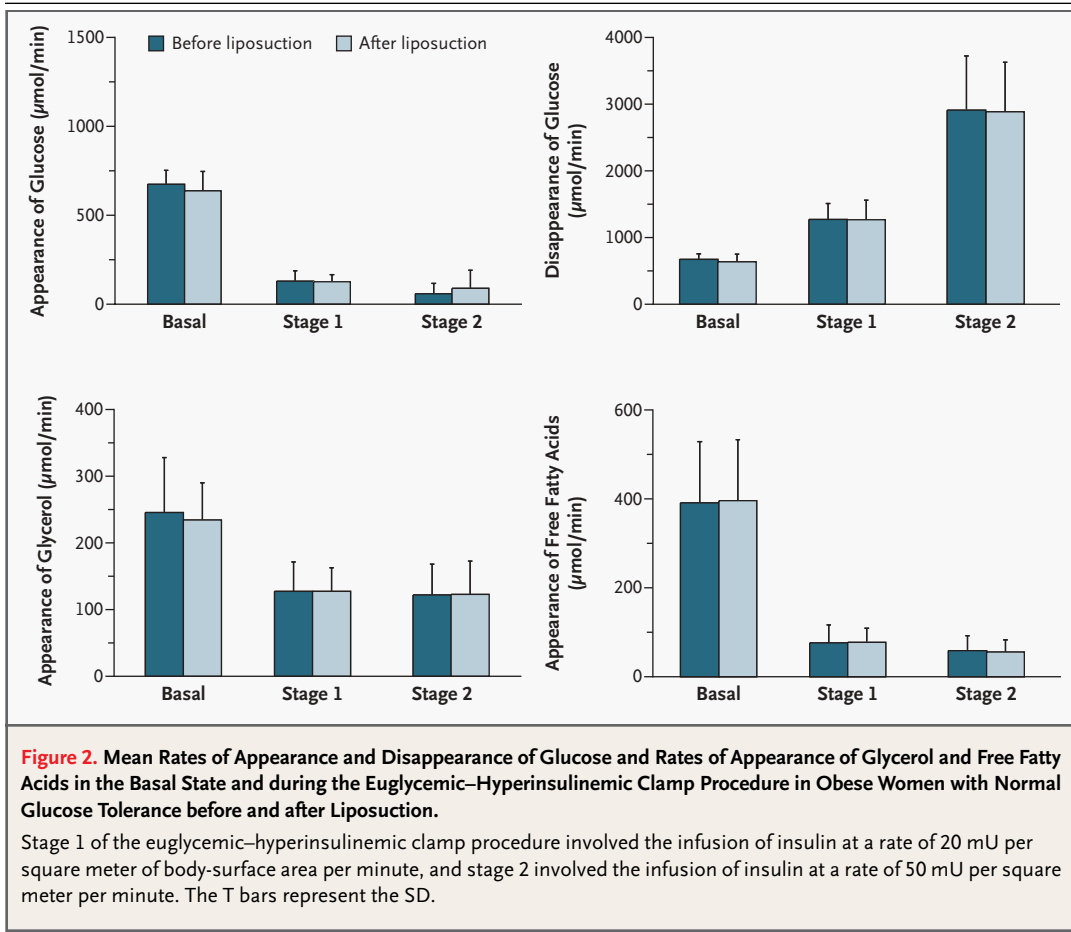
* Plus-minus values are means ±SD. The measurements were made within 9 days before liposuction and again 10 to 12 weeks after liposuction. CI denotes confidence interval, minus signs decreases, and plus signs increases.

† Values were obtained from six subjects in each group.

insulin sensitivity in skeletal muscle (assessed as the stimulation of glucose uptake), in the liver (assessed as the suppression of glucose production), or adipose tissue (assessed as the suppression of lipolysis). In addition, liposuction had no significant effects on other risk factors for coronary heart disease, including blood pressure; fasting plasma glucose, insulin, and lipid concentrations; and concentrations of plasma markers of inflammation and insulin resistance (C-reactive protein, tumor necrosis factor α, interleukin-6, and adiponectin).

The amount of fat removed by liposuction in our

subjects is equivalent to the weight loss achieved by optimal behavioral and pharmacologic treatments.³ A total weight loss of approximately 12 percent of body weight would be required to achieve the fat loss resulting from liposuction in our study subjects, because about 75 percent of the decrease in body-mass that occurs by dieting is due to loss of body fat.¹⁷ This amount of weight loss usually results in marked improvement in the metabolic abnormalities associated with obesity and improves insulin sensitivity,¹⁸ blood pressure,¹⁹ and concentrations of serum lipids²⁰ and circulating markers

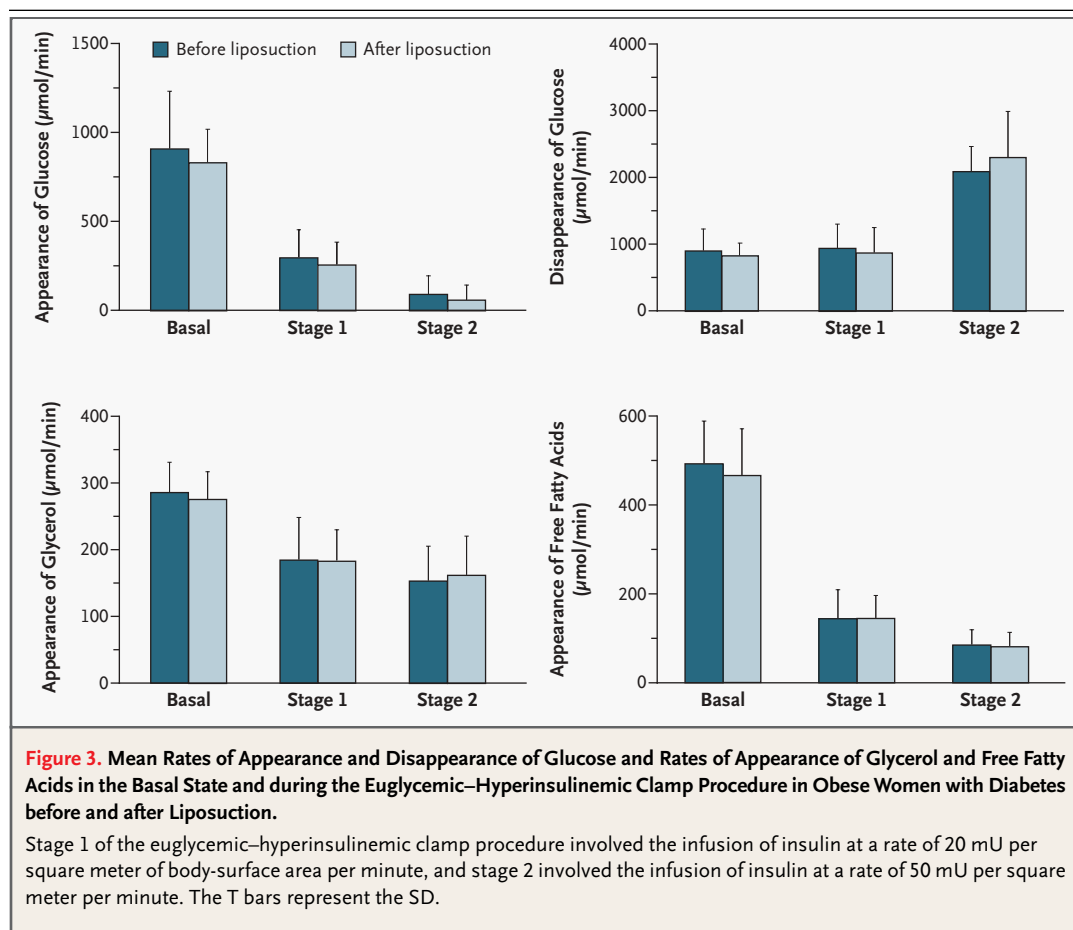


of inflammation.²¹ Therefore, it is striking that the amount of fat loss achieved by liposuction in our diabetic and nondiabetic subjects did not improve any of these metabolic variables.

The absence of an apparent therapeutic effect of liposuction provides insight into the mechanism by which conventional therapy for obesity — namely, diet, pharmacotherapy, and bariatric surgery — improves insulin sensitivity. Our results suggest that induction of a negative energy balance, not simply a decrease in the mass of adipose tissue, is critical for achieving the metabolic benefits of weight loss. Even small amounts of weight loss induced by a negative energy balance affects many variables pertaining to body-fat composition and lipid metabolism — variables that probably contribute to the metabolic abnormalities associated with obesity.^{22–25} Weight loss decreases visceral fat mass,²⁶ intramyocellular fat,²⁷ intrahepatic fat,²⁸ fat-cell size,²⁹ and the rate of release of fatty acids from adipose tissue.³⁰ In contrast, liposuction removes sub-

cutaneous abdominal fat and reduces the total number of body fat cells, without altering visceral fat mass,³¹ the size of the remaining fat cells,¹⁰ intramyocellular fat, or intrahepatic fat.

The results of the present study also show that removing a large amount of abdominal subcutaneous fat by liposuction does not significantly affect the levels of circulating mediators of inflammation that are probably involved in the development of insulin resistance and coronary heart disease.³² Adipose tissue is now recognized as an important endocrine organ that produces several bioactive proteins, including interleukin-6, tumor necrosis factor α , and adiponectin. Interleukin-6 and tumor necrosis factor α can cause insulin resistance and atherosclerosis by impairing insulin signaling, stimulating lipolysis and fatty acid release, increasing hepatic synthesis of C-reactive protein, and increasing systemic inflammation,^{32–34} whereas the production of adiponectin by adipose tissue can improve insulin sensitivity and inhibit vascular



inflammation.^{35,36} Fat loss achieved by conventional obesity treatments decreases the plasma concentrations of C-reactive protein, interleukin-6, and tumor necrosis factor α ^{37,38} and increases the concentration of adiponectin³⁹; in contrast, liposuction in our subjects did not significantly change the plasma concentrations of any of these markers. However, fat removal by liposuction did decrease the plasma leptin concentration, which is a marker of adipose-tissue mass.⁴⁰ These results suggest that a negative energy balance influences adipocyte and monocyte activation and the gene expression of selected cytokines, but that long-term leptin production is influenced primarily by total fat mass.

The results of the present study suggest that abdominal liposuction should not, by itself, be considered a clinical therapy for obesity. Aspiration of large amounts of subcutaneous abdominal fat in women with abdominal obesity may have cosmetic benefits, but the procedure does not significantly

improve insulin sensitivity in the liver, skeletal muscle, or adipose tissue; serum concentrations of markers of inflammation; or other risk factors for coronary heart disease. These findings offer important insights into the mechanisms responsible for the metabolic benefits observed with moderate diet-induced weight loss, which decreases hepatic and muscle fat content, fat-cell size, visceral fat mass, and circulating concentrations of proinflammatory cytokines. The effects of a negative energy balance on specific endogenous triglyceride depots and inflammation, which are not altered by liposuction, may be necessary to achieve many of the clinical benefits of therapy for obesity.

Supported by grants (HD 01459, DK 37948, RR-00954 [to the Biomedical Mass Spectrometry Resource], RR-00036 [to the General Clinical Research Center], and DK 56341 [to the Clinical Nutrition Research Unit]) from the National Institutes of Health.

We are indebted to the nursing staff of the General Clinical Research Center for their help in performing the studies, to Freida Custodio and Junyoung Kwon for their technical assistance, and to the subjects for their participation in the study.

REFERENCES

1. Kissebah AH, Videlingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 1982;54:254-60.
2. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 1995;96:88-98.
3. Klein S, Wadden T, Sugerman HJ. AGA technical review on obesity. *Gastroenterology* 2002;123:882-932. [Erratum, *Gastroenterology* 2002;123:1752.]
4. Matarasso A, Hutchinson OH. Liposuction. *JAMA* 2001;285:266-8.
5. Gonzalez-Ortiz M, Robles-Cervantes JA, Cardenas-Camarena L, Bustos-Saldana R, Martinez-Abundis E. 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* 2002;34:446-9.
6. Giese SY, Bulan EJ, Commons GW, Spear SL, Yanovski JA. Improvements in cardiovascular risk profile with large-volume liposuction: a pilot study. *Plast Reconstr Surg* 2001;108:510-9.
7. Samdal F, Birkeland KI, Ose L, Amland PF. Effect of large-volume liposuction on sex hormones and glucose- and lipid metabolism in females. *Aesthetic Plast Surg* 1995;19:131-5.
8. The American Society for Aesthetic Plastic Surgery. *Cosmetic Surgery National Data Bank 2002 statistics*. (Accessed April 20, 2004, at <http://www.surgery.org/press/statistics-2002.asp>.)
9. Commons GW, Halperin B, Chang CC. Large-volume liposuction: a review of 631 consecutive cases over 12 years. *Plast Reconstr Surg* 2001;108:1753-63.
10. Lambert EV, Hudson DA, Bloch CE, Koeslag JH. Metabolic response to localized surgical fat removal in nonobese women. *Aesthetic Plast Surg* 1991;15:105-10.
11. Berntorp E, Berntorp K, Brorson H, Frick K. Liposuction in Dercum's disease: impact on haemostatic factors associated with cardiovascular disease and insulin sensitivity. *J Intern Med* 1998;243:197-201.
12. Trott SA, Beran SJ, Rohrich RJ, Kenkel JM, Adams WP Jr, Klein KW. Safety considerations and fluid resuscitation in liposuction: an analysis of 53 consecutive patients. *Plast Reconstr Surg* 1998;102:2220-9.
13. Horowitz JF, Coppack SW, Paramore D, Cryer PE, Zhao G, Klein S. Effect of short-term fasting on lipid kinetics in lean and obese women. *Am J Physiol* 1999;276:E278-E284.
14. Horowitz JF, Coppack SW, Klein S. Whole body and adipose tissue glucose metabolism in response to short-term fasting in lean and obese women. *Am J Clin Nutr* 2001;73:517-22.
15. Steele R. Influences of glucose loading and of injected insulin on hepatic glucose output. *Ann NY Acad Sci* 1959;82:420-30.
16. Mladick RA. Lipoplasty of the calves and ankles. *Plast Reconstr Surg* 1990;86:84-93.
17. Ballor DL, Poehlman ET. Exercise-training enhances fat-free mass preservation during diet-induced weight loss: a meta-analytical finding. *Int J Obes Relat Metab Disord* 1994;18:35-40.
18. Uusitupa M, Lindi V, Louheranta A, Salopuro T, Lindstrom J, Tuomilehto J. Long-term improvement in insulin sensitivity by changing lifestyles of people with impaired glucose tolerance: 4-year results from the Finnish Diabetes Prevention Study. *Diabetes* 2003;52:2532-8.
19. Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, phase II. *Ann Intern Med* 2001;134:1-11.
20. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr* 1992;56:320-8.
21. Ziccardi P, Nappo F, Giugliano G, et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* 2002;105:804-9.
22. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. *Eur J Clin Invest* 2002;32:Suppl 3:14-23.
23. Krssak M, Falk Petersen K, Dresner A, et al. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a ¹H NMR spectroscopy study. *Diabetologia* 1999;42:113-6. [Errata, *Diabetologia* 1999;42:386, 1269.]
24. Seppala-Lindroos A, Vehkavaara S, Hakkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. *J Clin Endocrinol Metab* 2002;87:3023-8.
25. Weyer C, Foley JE, Bogardus C, Tataranni PA, Pratley RE. Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. *Diabetologia* 2000;43:1498-506.
26. Purnell JQ, Kahn SE, Albers JJ, Nevin DN, Brunzell JD, Schwartz RS. Effect of weight loss with reduction of intra-abdominal fat on lipid metabolism in older men. *J Clin Endocrinol Metab* 2000;85:977-82.
27. Goodpaster BH, Theriault R, Watkins SC, Kelley DE. Intramuscular lipid content is increased in obesity and decreased by weight loss. *Metabolism* 2000;49:467-72.
28. Tiikkainen M, Bergholm R, Vehkavaara S, et al. Effects of identical weight loss on body composition and features of insulin resistance in obese women with high and low liver fat content. *Diabetes* 2003;52:701-7.
29. Knittle JL, Ginsberg-Fellner F. Effect of weight reduction on in vitro adipose tissue lipolysis and cellularity in obese adolescents and adults. *Diabetes* 1972;21:754-61.
30. Klein S, Luu K, Gasic S, Green A. Effect of weight loss on whole body and cellular lipid metabolism in severely obese humans. *Am J Physiol* 1996;270:E739-E745.
31. Matarasso A, Kim RW, Kral JG. The impact of liposuction on body fat. *Plast Reconstr Surg* 1998;102:1686-9.
32. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab* 2000;11:327-32.
33. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am J Physiol Endocrinol Metab* 2001;280:E745-E751.
34. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 2000;148:209-14.
35. Ouchi N, Kihara S, Arita Y, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF- κ B signaling through a cAMP-dependent pathway. *Circulation* 2000;102:1296-301.
36. Okamoto Y, Kihara S, Ouchi N, et al. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 2002;106:2767-70.
37. Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003;289:1799-804.
38. Dandona P, Weinstock R, Thusu K, Abdel-Rahman E, Aljada A, Wadden T. Tumor necrosis factor- α in sera of obese patients: fall with weight loss. *J Clin Endocrinol Metab* 1998;83:2907-10.
39. Yang WS, Lee WJ, Funahashi T, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 2001;86:3815-9. [Erratum, *J Clin Endocrinol Metab* 2002;87:1626.]
40. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;334:292-5.

Copyright © 2004 Massachusetts Medical Society.