Reversal of Nonalcoholic Hepatic Steatosis, Hepatic Insulin Resistance, and Hyperglycemia by Moderate Weight Reduction in Patients With Type 2 Diabetes

Kitt Falk Petersen,[1] Sylvie Dufour,[1,2] Douglas Befroy,[1] Michael Lehrke,[3] Rosa E. Hendler,[1] and Gerald I. Shulman[1,2,4]

To examine the mechanism by which moderate weight reduction improves basal and insulin-stimulated rates of glucose metabolism in patients with type 2 diabetes, we used ^{1}H magnetic resonance spectroscopy to assess intrahepatic lipid (IHL) and intramyocellular lipid (IMCL) content in conjunction with hyperinsulinemic-euglycemic clamps using [6,6-$^2H_2$]glucose to assess rates of glucose production and insulin-stimulated peripheral glucose uptake. Eight obese patients with type 2 diabetes were studied before and after weight stabilization on a moderately hypocaloric very-low-fat diet (3%). The diabetic patients were markedly insulin resistant in both liver and muscle compared with the lean control subjects. These changes were associated with marked increases in IHL (12.2 ± 3.4 vs. 0.6 ± 0.1%; $P = 0.02$) and IMCL (2.0 ± 0.3 vs. 1.2 ± 0.1%; $P = 0.02$) compared with the control subjects. A weight loss of only ~8 kg resulted in normalization of fasting plasma glucose concentrations (8.8 ± 0.5 vs. 6.4 ± 0.3 mmol/l; $P < 0.0005$), rates of basal glucose production (193 ± 7 vs. 153 ± 10 mg/min; $P < 0.0005$), and the percentage suppression of hepatic glucose production during the clamp (29 ± 22 vs. 99 ± 3%; $P = 0.003$). These improvements in basal and insulin-stimulated hepatic glucose metabolism were associated with an 81 ± 4% reduction in IHL ($P = 0.0009$) but no significant change in insulin-stimulated peripheral glucose uptake or IMCL (2.0 ± 0.3 vs. 1.9 ± 0.3%; $P = 0.21$). In conclusion, these data support the hypothesis that moderate weight loss normalizes fasting hyperglycemia in patients with poorly controlled type 2 diabetes by mobilizing a relatively small pool of IHL, which reverses hepatic insulin resistance and normalizes rates of basal glucose production, independent of any changes in insulin-stimulated peripheral glucose metabolism. *Diabetes* 54:603–608, 2005

From the [1]Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut; the [2]Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, Connecticut; the [3]Department of Internal Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and the [4]Department of Cellular & Molecular Physiology, Yale University School of Medicine, New Haven, Connecticut.

Address correspondence and reprint requests to Kitt Falk Petersen, MD, Yale University School of Medicine, Department of Internal Medicine, 300 Cedar St., S263 TAC, P.O. Box 9812, New Haven, CT 06520-8020. E-mail: kitt.petersen@yale.edu.

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APE, atom percent enrichment; GCRC, General Clinical Research Center; IHL, intrahepatic lipid; IL-6, interleukin-6; IMCL, intramyocellular lipid; IRS, insulin receptor substrate; MRS, magnetic resonance spectroscopy.

Previous studies have demonstrated that relatively modest weight reduction in obese patients with poorly controlled type 2 diabetes can markedly reduce plasma glucose concentrations, but the mechanism responsible for this phenomenon is not known (1). Henry et al. (1) showed that a weight loss of 16.8 ± 2.7 kg led to a reduction in fasting plasma glucose concentrations from 15.3 ± 1.2 to 6.8 ± 0.4 mmol/l and that the individual fasting glucose concentrations were highly correlated with rates of basal hepatic glucose production.

We hypothesized that a relatively small pool of intrahepatic lipid (IHL) might be responsible for the hepatic insulin resistance and increased rates of glucose production in patients with poorly controlled type 2 diabetes and that hepatic steatosis and hepatic insulin resistance would reverse with modest weight reduction before any changes in peripheral insulin resistance and intramyocellular lipid (IMCL) content.

To test these hypotheses, we used ^{1}H magnetic resonance spectroscopy (MRS) to noninvasively assess IHL and IMCL content in eight obese type 2 diabetic patients before and after weight stabilization on a hypocaloric diet, which was maintained until they reached normal fasting plasma glucose concentrations. Hepatic glucose production and insulin sensitivity of liver and muscle were assessed with a hyperinsulinemic (~480 pmol/l)-euglycemic (~6.0 mmol/l) clamp, using [6,6-$^2H_2$]glucose. In addition, rates of net hepatic glycogenolysis and gluconeogenesis were assessed in a subgroup of patients before and after weight loss by ^{13}C MRS as previously described (2).

RESEARCH DESIGN AND METHODS

Eight healthy, nonsmoking, obese type 2 diabetic patients (five men and three women; 47 ± 3 years of age) were studied (Table 1). At the time of study enrollment, three patients' diabetes was controlled with diet and the five others were taking sulfonylurea agents to control their diabetes. They did not take any other medications. The patients discontinued this antidiabetic diet/medication 10 days before the baseline study. The control group consisted of 10 lean, nonsmoking, healthy volunteers (5 men and 5 women; 30 ± 2 years of age) who were studied once at baseline. The control subjects were not taking any medications. All of the study participants had a sedentary lifestyle, and none were engaged in any regular exercise regimens. For 3 days before each of the studies, the subjects were given an isocaloric diet (35 kcal/kg; 60% carbohydrate, 20% protein, 20% fat) that was prepared by the metabolic kitchen of the Yale/New Haven Hospital General Clinical Research Center (GCRC). The calories in this diet were divided evenly among the three daily meals. At 4 P.M. on the 3rd day, they were admitted to the GCRC, given

TABLE 1
Body weight, BMI, and body composition in control subjects and patients with type 2 diabetes before and after weight loss

	Control	*P* value, control vs. before weight loss	Before weight loss	After weight loss	*P* value, before vs. after weight loss
n	10		8	8	
Body weight (kg)	77 ± 4	NS	86 ± 3	78 ± 3	0.002
BMI (kg/m^2)	25.2 ± 1.0	<0.005	30.1 ± 0.9	27.5 ± 0.8	0.002
Fat mass (kg)	18.5 ± 2.1	NS	23.6 ± 2.1	20.0 ± 1.6	0.009
Fat mass (%)	24.3 ± 2.6	NS	27.6 ± 2.5	25.7 ± 2.2	0.02
Lean body mass (kg)	58.1 ± 3.6	NS	62.0 ± 3.2	58.5 ± 3.2	0.0003
Truncal fat mass (kg)	7.60 ± 1.13	<0.005	13.09 ± 1.22	10.72 ± 0.80	0.007

Data are means ± SE.

dinner at 6 P.M., and then fasted until the end of the baseline study the following day.

Body composition. On the day of admission, dual energy X-ray absorptiometry scan (Hologic QDR-4500 W, Bedford, MA) was performed with the subject lying in the supine position as previously described (3).

MRS measurements of liver and muscle triglyceride content. After an overnight fast, the subjects were brought to the Yale-Magnetic Resonance Center and positioned in a 2.1T NMR Biospec system (Bruker Instruments, Billerica, MA) spectrometer for measurement of lipid content in the liver and the right soleus muscle. After percussion of the liver borders, a circular ^{1}H observation coil (12 cm) was placed rigidly over the lateral aspect of the abdomen and localized ^{1}H magnetic resonance spectra of the liver were obtained. Placement of the liver volume of interest (15 mm^3) was confirmed by imaging the liver with a multislice gradient echo sequence. Before each measurement, the water signal was optimized during a shimming procedure and localized ^{1}H spectra were collected using a PRESS sequence (repetition time of 3 s, echo time of 24.1 ms, 8,192 data points over 5,000-Hz spectral width and 64 scans) complemented by a spatially localized suppression pulse centered into the adipose tissue (4). A Lorentzian filter of 5 Hz was applied before Fourier transformation and manual phase correction. Hepatic triglyceride content was calculated from the area of intrahepatic CH_2 resonance relative to the area of the water resonance, using the integration routine of Paravision software (Bruker Instruments) and then expressed as a percentage of water content. Localized ^{1}H magnetic resonance spectra of the soleus muscle to assess IMCL content were obtained as previously described (4).

Indirect calorimetry. Continuous indirect calorimetry was performed with a SensorMedics calorimeter (SensorMedics, Anaheim, CA) as previously described (5,6).

Euglycemic-hyperinsulinemic clamp. On the morning of the study, after the overnight fast and the MRS measurements of lipid in liver and muscle, a catheter was placed in an antecubital vein for infusions and a retrograde catheter was placed in a hand vein for blood withdrawal. The hand was kept warm in a heated box at 55°C to "arterialize" the blood. Basal rates of glucose turnover were assessed after a 180-min baseline period with a primed-continuous (3.4 mg · m^{-2} · min^{-1}) infusion of [6,6-$^2H_2$]glucose (99% atom percent enrichment [APE]; Cambridge Isotopes Laboratories, Andover, MA). The priming dose was corrected for ambient fasting plasma glucose levels as previously described (7). After this baseline period, a hyperinsulinemic-euglycemic clamp was initiated. A primed-constant infusion of insulin (40 mU · m^{-2} · min^{-1}; U-100 Humulin-R; Eli Lilly, Indianapolis, IN) was given, and when plasma glucose concentrations had decreased to 6.1 ± 0.3 mmol/l, the basal 99% APE [6,6-$^2H_2$]glucose infusion was stopped and for 240 min plasma glucose concentrations were maintained with a variable D-20 glucose infusion that contained 3% [6,6-$^2H_2$]glucose (7).

Rates of net hepatic glycogenolysis and gluconeogenesis. In a subgroup of three diabetic patients, the contributions of net hepatic glycogenolysis and gluconeogenesis were assessed before and after weight loss. At 6 P.M. on the day of admission, a 1,000-kcal liquid dinner that contained 60% carbohydrate (80% of which was glucose), 20% fat, and 20% protein was given to ensure maximum hepatic glycogen stores and uniform meal absorption (2). The meal was consumed over 15 min, and the patients then fasted overnight until the end of the study the next day.

From 11 P.M. to midnight and again from 6 to 7 A.M., hepatic glycogen concentrations were measured using ^{13}C nuclear MRS as previously described (2). The liver glycogen measurements were followed by measurements of lipid content in the liver and the right soleus muscles.

Weight loss diet. After completion of the baseline studies, the patients with type 2 diabetes started a weight-loss regimen. The diet consisted of a liquid diet formula (Medibase II; Advanced Healthcare, Avadyne, Monterey, CA) with 50% carbohydrate, 43% protein, 3% fat, and 12 g of dietary fiber, which was supplemented with raw fruit and vegetables to ~1,200 kcal/day. This diet contained all essential nutrients and vitamins. The weekly visits for ^{1}H MRS of IHL and IMCL were combined with recording of body weight and vital signs; measurements of plasma electrolytes, glucose, and insulin concentrations; and nutritional counseling. The weight-loss program continued until achievement of normoglycemia (between 3 and 12 weeks) and was followed by 4 weeks of weight stabilization on an isocaloric diet of regular food similar to the diet given before the start of the baseline study (35 kcal/kg; 60% carbohydrate, 20% protein, 20% fat). The calories were divided evenly among the three daily meals. At 4 P.M. on the day before the follow-up study, the diabetic patients were admitted to the GCRC, given dinner at 6 P.M., and then fasted until the end of the follow-up study the next day.

Analytical procedures. Plasma glucose concentrations were measured using a YSI STAT 2700 Analyzer (YSI, Yellow Springs, CA). Plasma immunoreactive insulin, glucagon, leptin, adiponectin, and resistin concentrations were measured using antibody radioimmunoassay kits (Linco Research, St. Charles, MO). Plasma concentrations of fatty acids were determined using a microfluorimetric method (8). Plasma tumor necrosis factor-α and interleukin-6 (IL-6) were measured by Quantine High Sensitivity kits (R&D Systems, Minneapolis, MN).

Gas chromatography–mass spectrometry analysis. ^{2}H APE in plasma glucose was determined by gas chromatography–mass spectrometry using a Hewlett-Packard (Palo Alto, CA) 5890 gas chromatograph interfaced with a Hewlett-Packard 5971A Mass Selective detector as described (4).

Data analysis. Differences between the control subjects and the type 2 diabetic patients were assessed by Student's *t* test, and differences between pre– and post–weight loss effects were assessed by paired *t* tests. All data are presented as means ± SE.

RESULTS

Before the weight-loss regimen, all diabetic patients were in moderate control as reflected by increased HbA_{1c} (7.0 ± 0.4%), fasting hyperglycemia, hypertriglyceridemia, and hypercholesterolemia (Table 2). Rates of fasting glucose production were 42% higher in the diabetic patients than in the control subjects (Fig. 1*A*). The diabetic patients were severely insulin resistant as reflected by very low rates of glucose infusion required to maintain euglycemia during the hyperinsulinemic-euglycemic clamp (diabetic 4.8 ± 1.2 mg · kg LBM^{-1} · min^{-1} vs. control 10.9 ± 0.6 mg · kg LBM^{-1} · min^{-1}; $P = 0.0002$) as well as by a marked reduction in insulin-stimulated whole-body glucose metabolism (Fig. 1*B*). This was associated with a 70% increase in IMCL (Fig. 1*E*). Furthermore, the diabetic patients had severe hepatic insulin resistance as reflected by decreased insulin suppression of glucose production during the hyperinsulinemic clamp (diabetic 29 ± 22% vs. control 99 ± 3%; $P = 0.003$; Fig. 1*C*). These alterations were associated with severe hepatic steatosis in all of the diabetic patients (Fig. 1*D*). Hepatic enzymes, ALT and AST, were normal (24 ± 3 and 21 ± 2 units/l, respectively; normal range 0–35 units/l).

There were no differences between basal rates of glu-

TABLE 2
Fasting plasma metabolite concentrations in control subjects and patients with type 2 diabetes before and after weight loss

	Control	*P* value, control vs. before weight loss	Before weight loss	After weight loss	*P* value, before vs. after weight loss
n	10		8	8	
Glucose (mmol/l)	4.9 ± 0.2	<0.0001	8.8 ± 0.5	6.4 ± 0.3	0.00037
Insulin (pmol/l)	60 ± 6	NS	174 ± 48	66 ± 6	0.03
C-peptide (pmol/l)	ND	ND	1.14 ± 0.36	0.73 ± 0.06	NS
Glucagon (pg/ml)	57 ± 6	NS	77 ± 7	58 ± 6	0.02
Cortisol (μg/dl)	19 ± 3	NS	16 ± 1	12 ± 2	NS
Total cholesterol (mg/dl)	168 ± 8	NS	202 ± 18	177 ± 17	<0.05
HDL (mg/dl)	57 ± 3	NS	40 ± 2	36 ± 3	NS
LDL (mg/dl)	91 ± 5	NS	119 ± 17	102 ± 10	NS
Triglycerides (mg/dl)	104 ± 16	0.01	212 ± 38	187 ± 58	NS
Free fatty acids (mmol/l)	0.49 ± 0.07	NS	0.49 ± 0.05	0.49 ± 0.05	NS
Leptin (pg/ml)	4.9 ± 1.0	NS	11.9 ± 2.5	7.5 ± 1.9	0.01
Resistin (ng/ml)	25.5 ± 1.4	NS	24.5 ± 2.5	21.8 ± 1.7	NS
IL-6 (pg/ml)	ND	ND	0.49 ± 0.16	0.81 ± 0.29	NS
Adiponectin (μg/ml)	14.3 ± 2.0	0.00146	5.8 ± 1.1	5.1 ± 0.6	NS
TNF-α (pg/ml)	ND	ND	1.524 ± 0.071	1.347 ± 0.047	0.03

Data are means ± SE.

cose and lipid oxidation as compared with the control subjects and no significant changes after the weight loss (Table 3). During the clamp study, rates of glucose oxidation were 47 ± 11% lower ($P = 0.0006$) and rates of lipid oxidation were 167 ± 44% higher ($P < 0.0001$) than in the control subjects.

After an average 7 weeks of the diet and an average weight loss of 8.0 ± 1.4 kg (range 3.3–16.0 kg), or 8 ± 2% of the initial body weight (Table 1), there was a marked reduction in the fasting plasma glucose concentration (Table 2). The reduction in fasting plasma glucose concentration and body weight were associated with a 53 ± 7 and 32 ± 7% decreases in mean fasting plasma insulin and glucagon concentrations, respectively (Table 2). There were no significant changes in serum ALT and AST with the weight loss (17 ± 3 and 20 ± 3 units/l, respectively).

After the weight reduction, plasma concentrations of total cholesterol decreased by 13 ± 4% ($P < 0.05$). HDL, LDL, and triglycerides all tended to decrease in a similar manner after completion of the weight-loss program, but these changes were not significant (Table 2).

This improvement in glycemic control could be attributed to a large increase in whole-body insulin sensitivity, as reflected by an approximately twofold increase in the rate of glucose infusion required to maintain euglycemia (7.6 ± 1.2 vs. 4.8 ± 1.2 mg · kg LBM^{-1} · min^{-1}; $P = 0.01$), although there were no changes in the rate of insulin-stimulated whole-body glucose metabolism (Fig. 1*B*). In contrast, there was a marked improvement in hepatic insulin responsiveness, as reflected by an increase of insulin suppression of glucose production to 93 ± 5% during the clamp compared with 29 ± 22% before the weight loss ($P = 0.04$; Fig. 1*C*). These changes in hepatic sensitivity were associated with an 81 ± 4% reduction in hepatic triglyceride content ($P = 0.009$; Fig. 1*D*) to nearly normal levels (2.2 ± 0.8%; $P < 0.005$ versus before weight loss). There was no significant correlation between hepatic triglyceride content and insulin suppression of hepatic glucose production. In contrast to the large decrease in IHL content, the weight loss and improvement in hepatic insulin sensitivity were not associated with any changes in the IMCL content (Fig. 1*E*).

Energy expenditure was lower in all of the diabetic patients after weight loss (1,754 ± 61 vs. 1,544 ± 68 kcal/day; $P < 0.001$). The fasting respiratory quotient was unaffected by the weight loss (before weight loss 0.82 ± 0.02 vs. after weight loss 0.80 ± 0.01; NS).

Rates of net hepatic glycogenolysis and gluconeogenesis. To examine the mechanism responsible for the reduced rates of hepatic glucose production after weight reduction, we measured rates of net hepatic glycogenolysis and gluconeogenesis in a subgroup of three diabetic patients. Before the weight reduction, the increased rates of glucose production could be entirely accounted for by increased rates of gluconeogenesis (185.7 ± 18.1 mg/min). After weight loss, rates of net hepatic glycogenolysis increased (7.1 ± 3.4 vs. 27.4 ± 1.5 mg/min; $P = 0.03$), and the reduced rates of glucose production could be attributed to a reduction in the rates of gluconeogenesis (153.4 ± 14.0 mg/min; $P = 0.02$ versus before weight loss).

DISCUSSION

All of the type 2 diabetic patients manifested severe hepatic and peripheral insulin resistance associated with hepatic steatosis and increased IMCL. A moderate weight loss of ~8 kg, or ~8% of their body weight, normalized fasting plasma glucose concentrations and was associated with an ~10% decrease in plasma cholesterol concentrations. This improved glycemic control could be attributed to a marked improvement in their insulin responsiveness, as reflected by an approximately fourfold increase in the glucose infusion rate required to maintain euglycemia during the hyperinsulinemic-euglycemic clamp. To ascertain the mechanism for the improved insulin responsiveness, we also assessed rates of hepatic and peripheral glucose metabolism using deuterated glucose and found that the weight reduction normalized insulin suppression of hepatic glucose production but had no effects on peripheral insulin sensitivity. This improvement in hepatic

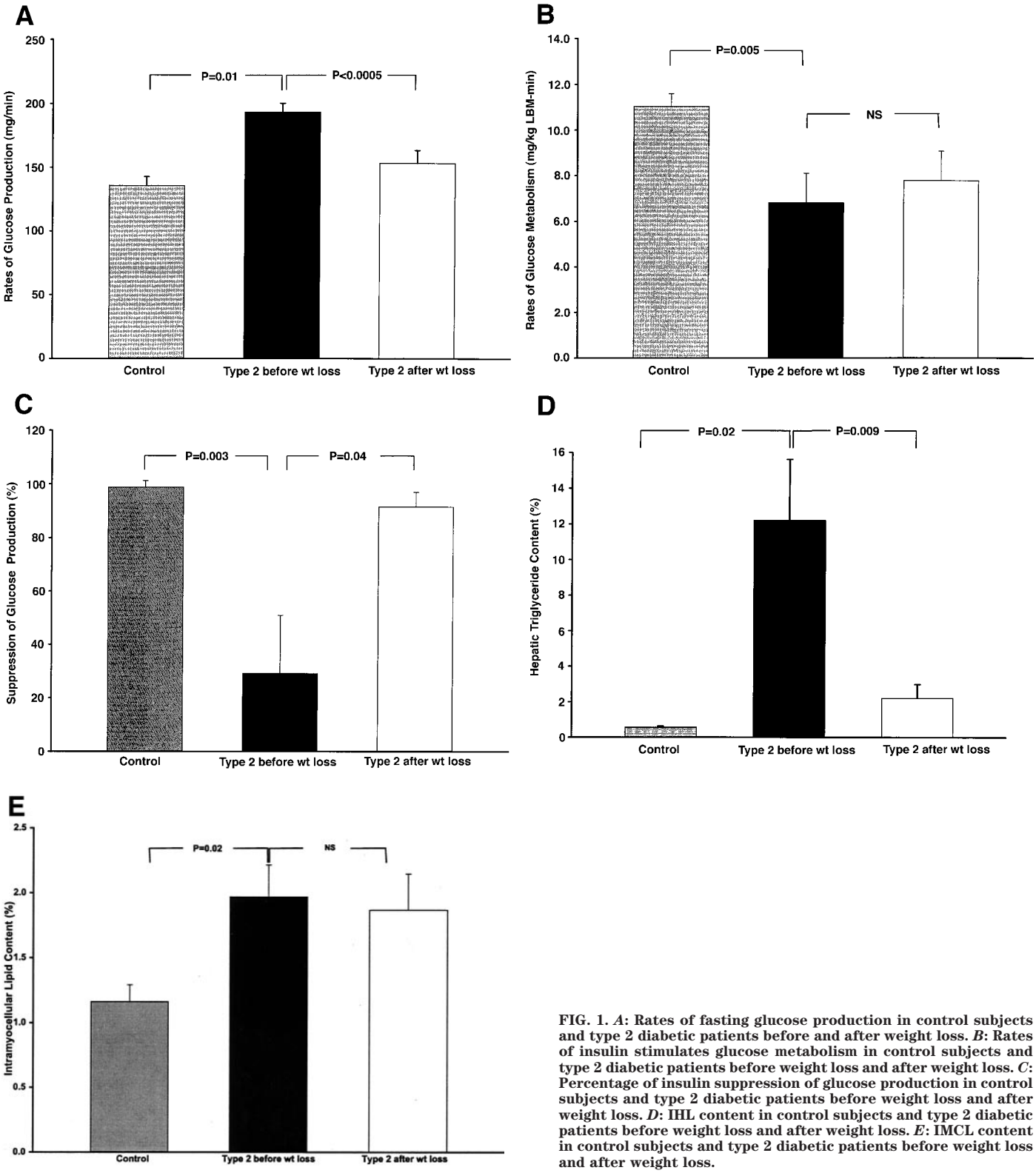

FIG. 1. *A*: **Rates of fasting glucose production in control subjects and type 2 diabetic patients before and after weight loss.** *B*: **Rates of insulin stimulates glucose metabolism in control subjects and type 2 diabetic patients before weight loss and after weight loss.** *C*: **Percentage of insulin suppression of glucose production in control subjects and type 2 diabetic patients before weight loss and after weight loss.** *D*: **IHL content in control subjects and type 2 diabetic patients before weight loss and after weight loss.** *E*: **IMCL content in control subjects and type 2 diabetic patients before weight loss and after weight loss.**

insulin sensitivity was associated with an ~80% reduction of hepatic triglyceride content. In contrast, there was no change in IMCL content with weight reduction. Previous studies by our group (3,4,9,10) and others (11–13) have demonstrated a strong relationship between hepatic triglyceride content and hepatic insulin resistance. The mechanism by which hepatic steatosis causes hepatic insulin resistance is unknown but may be related to activation of a serine kinase cascade by accumulation of intracellular fatty acid metabolites that in turn inhibit insulin signaling at the level of the insulin receptor and insulin receptor substrates (IRS) 1 and 2 (IRS-1 and IRS-2) (14). Studies in transgenic mice with hepatic steatosis as a result of liver-specific overexpression of lipoprotein lipase (9) or mice with lipodystrophy and hepatic steatosis (15) have shown that intracellular accumulation of fatty acid–

TABLE 3
Rates of glucose oxidation, lipid oxidation, and RQ in the basal state and during the euglycemic-hyperinsulinemic clamp in control subjects and patients with type 2 diabetes before and after weight loss

	Control	*P* value, control vs. type 2 diabetes before weight loss	Type 2 diabetes before weight loss	Type 2 diabetes after weight loss	*P* value, type 2 diabetes before vs. after weight loss
n	10		8	8	
Basal glucose oxidation ($mg \cdot kg\ LBM^{-1} \cdot min^{-1}$)	1.01 ± 0.13	NS	1.06 ± 0.26	0.85 ± 0.13	NS
Basal lipid oxidation ($mg \cdot kg\ LBM^{-1} \cdot min^{-1}$)	4.60 ± 0.36	NS	4.03 ± 0.66	4.63 ± 0.49	NS
Basal RQ	0.81 ± 0.01	NS	0.82 ± 0.02	0.80 ± 0.01	NS
Clamp glucose oxidation ($mg \cdot kg\ LBM^{-1} \cdot min^{-1}$)	3.05 ± 0.52	0.014	3.85 ± 0.55	3.06 ± 0.68	NS
Clamp lipid oxidation ($mg \cdot kg\ LBM^{-1} \cdot min^{-1}$)	0.89 ± 0.21	<0.00001	1.40 ± 0.17	1.57 ± 0.21	NS
Clamp RQ	0.93 ± 0.01	0.018	0.85 ± 0.02	0.87 ± 0.02	NS

Data are means ± SE. LBM, lean body mass; RQ, respiratory quotient.

derived metabolites, such as long-chain fatty acyl CoAs, results in reduced insulin activation of IRS-2–associated phosphatidylinositol 3-kinase activity (9,16). More recent studies that have examined this question have shown that 3 days of high-fat feeding in rats resulted in hepatic steatosis–associated and liver-specific insulin resistance. These changes were associated with increases in hepatic fatty acyl CoAs, reduced insulin activation of IRS-1– and IRS-2–associated phosphatidylinositol 3-kinase, activation of protein kinase Cε, and increased gluconeogenesis (10). Furthermore, all of these changes, including the hepatic steatosis, were reversed by treating the rats with a low dose of the mitochondrial uncoupling agent 2,4 dinitrophenol (10).

Rates of gluconeogenesis were assessed in a subgroup of type 2 diabetic patients before and after weight loss. Before weight loss, these patients manifested increased rates of glucose production, and, consistent with previous studies (17–19), this increased glucose production could be attributed to increased rates of gluconeogenesis. After weight reduction, the normalization of rates of glucose production could be attributed entirely to a reduction in gluconeogenesis.

Recent studies have demonstrated a potentially important role for circulating concentrations of fatty acids (20–22) and adipocyte-derived cytokines (23–29) in altering insulin responsiveness in liver and muscle. Plasma concentrations of fatty acids, triglycerides, resistin, IL-6, adiponectin, and cortisol were not altered by the weight loss, suggesting that they do not play a major role in causing the reversal of hepatic insulin resistance in these individuals. In contrast, plasma concentrations of glucagon decreased by ~25% after weight reduction, suggesting a potentially important role of chronic hyperglucagonemia in promoting increased gluconeogenesis and hepatic insulin resistance in these patients with moderately to poorly controlled type 2 diabetes (17,30–32). Plasma concentrations of tumor necrosis factor-α also decreased by ~10% in these patients after weight loss and may also have played a minor contributing role in this process given its known ability to activate JNK1, which in turn will result in increased IRS-1 Ser^{307} phosphorylation (33). In contrast, plasma levels of leptin decreased with weight reduction, which is consistent with its well-established relationship with body fat mass (34).

These results have important clinical implications for treatment of patients with poorly controlled type 2 diabetes, demonstrating that a relatively modest weight reduction of <10% of their body weight leads to a marked reduction of IHL content, improved hepatic insulin sensitivity, and normalization of fasting plasma glucose concentrations. This modest weight reduction of ~8 kg (on a low fat [3%], moderately hypocaloric diet, defined as a diet that contains >800 kcal for adults) can be achieved by ~3 months of aggressive nutrition counseling, and it is psychologically an easier goal than the daunting task of achieving normal body weight. Furthermore, these data suggest that a relatively small pool of IHL, estimated by the ^{1}H MRS results to be <200 g (35), may be a major factor responsible for the hepatic insulin resistance and increased gluconeogenesis.

In summary, these studies demonstrate that moderate weight reduction (~8 kg) reverses hepatic steatosis and hepatic insulin resistance and normalizes basal rates of hepatic glucose production by decreasing gluconeogenesis. In contrast, there was no effect on peripheral insulin resistance, IMCL content, or circulating levels of resistin, IL-6, or adiponectin. These data support the hypothesis that a relatively small pool of IHL may be responsible for dysregulated hepatic glucose metabolism in patients with type 2 diabetes.

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