

LEPTIN-REPLACEMENT THERAPY FOR LIPODYSTROPHY

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ABSTRACT

Background The adipocyte hormone leptin is important in regulating energy homeostasis. Since severe lipodystrophy is associated with leptin deficiency, insulin resistance, hypertriglyceridemia, and hepatic steatosis, we assessed whether leptin replacement would ameliorate this condition.

Methods Nine female patients (age range, 15 to 42 years; eight with diabetes mellitus) who had lipodystrophy and serum leptin levels of less than 4 ng per milliliter (0.32 nmol per milliliter) received recombinant methionyl human leptin (recombinant leptin). Recombinant leptin was administered subcutaneously twice a day for four months at escalating doses to achieve low, intermediate, and high physiologic replacement levels of leptin.

Results During treatment with recombinant leptin, the serum leptin level increased from a mean (\pm SE) of 1.3 ± 0.3 ng per milliliter to 11.1 ± 2.5 ng per milliliter (0.1 ± 0.02 to 0.9 ± 0.2 nmol per milliliter). The absolute decrease in the glycosylated hemoglobin value was 1.9 percent (95 percent confidence interval, 1.1 to 2.7 percent; $P=0.001$) in the eight patients with diabetes. Four months of therapy decreased average triglyceride levels by 60 percent (95 percent confidence interval, 43 to 77 percent; $P<0.001$) and liver volume by an average of 28 percent (95 percent confidence interval, 20 to 36 percent; $P=0.002$) in all nine patients and led to the discontinuation of or a large reduction in antidiabetes therapy. Self-reported daily caloric intake and the measured resting metabolic rate also decreased significantly with therapy. Overall, recombinant leptin therapy was well tolerated.

Conclusions Leptin-replacement therapy improved glycemic control and decreased triglyceride levels in patients with lipodystrophy and leptin deficiency. Leptin deficiency contributes to the insulin resistance and other metabolic abnormalities associated with severe lipodystrophy. (N Engl J Med 2002;346:570-8.)

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THE adipocyte hormone leptin has a central role in energy homeostasis.¹ Serum leptin levels are directly proportional to adipocyte mass.² Normally, a low leptin level signals starvation and directs the body to adapt to this condition.³ One way to gain insight into the physiological importance of leptin in humans is to study

the conditions associated with its absence or deficiency.

Patients with a complete deficiency of leptin as a result of mutations in the leptin gene are morbidly obese from infancy and have a number of hormonal abnormalities, including insulin resistance and hypogonadotropic hypogonadism.⁴ Physiologic replacement with recombinant leptin for one year in one such patient led to a substantial weight reduction and an improvement in the hormonal abnormalities.⁵

Severe lipodystrophy, caused by a deficiency or destruction of adipose cells, is another state characterized by low leptin levels.⁶ Other abnormalities in this condition include hypertriglyceridemia and severe insulin resistance, which is usually accompanied by diabetes mellitus.^{6,7} There are several genetic and acquired forms of lipodystrophy in humans, and studies of a variety of genetically engineered animal models^{6,8} demonstrated that the metabolic abnormalities develop as a consequence of fat loss.⁹ Why is adipose tissue so vital to the prevention of the metabolic abnormalities? One hypothesis is that the adipocyte hormone leptin has a critical role in preventing the insulin resistance and hypertriglyceridemia of lipodystrophy. Interestingly, leptin-replacement therapy at a level meant to achieve physiologic levels led to a dramatic improvement in insulin resistance, hyperglycemia, hypertriglyceridemia, and hepatic steatosis in a mouse model of lipodystrophy.¹⁰ Therefore, we sought to determine whether such treatment would improve the insulin resistance, diabetes, and hypertriglyceridemia of patients with lipodystrophy.

METHODS**Patients**

Eligible patients had to have low serum leptin levels (less than 3 ng per milliliter [0.24 nmol per milliliter] in the case of male patients and less than 4 ng per milliliter [0.32 nmol per milliliter] in the case of female patients) in association with lipodystrophy and at least one of the following metabolic abnormalities: diabetes mellitus, defined according to the criteria of the American Diabetes Association¹¹; serum triglyceride levels (measured after an overnight fast) of more than 200 mg per deciliter (2.23 mmol per li-

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ter); and fasting serum insulin levels of more than 30 μU per milliliter (215 pmol per liter). Table 1 summarizes the base-line clinical characteristics of the nine patients treated in the study. The patients ranged from 15 to 42 years of age. All nine were female, although the study was open to both sexes. Five of the nine patients had congenital generalized lipodystrophy, or the Seip-Berardinelli syndrome, characterized by generalized fat loss from birth in association with other clinical criteria (Online Mendelian Inheritance in Man [OMIM]¹³ number 269700).¹⁴ One patient had Dunnigan's familial partial lipodystrophy (OMIM¹³ number 151660).^{15,16} The other three patients had acquired generalized lipodystrophy.

Study Design

The study was designed as a prospective, open-label study at the Diabetes Branch of the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (NIH) and the University of Texas Southwestern Medical Center in Dallas. Amgen (Thousand Oaks, Calif.) provided recombinant methionyl human leptin (recombinant leptin). Although Amgen provided the recombinant leptin, the data were held by the academic investigators. The response of each patient was compared with her base-line values. Because of the rarity and clinical variability of lipodystrophy syndromes, it was not feasible to include a randomized, placebo-treated control group. The study was approved by the institutional review boards of the study centers, and writ-

ten informed consent was obtained from all patients. The study was initiated in August 2000, and data collection was completed at the end of June 2001.

The patients were evaluated as inpatients before treatment and again after one, two, and four months of recombinant leptin therapy. All patients had been receiving stable doses of other medications for at least six weeks (range, six weeks to eight months) before they began to receive leptin-replacement therapy. During the study, the doses of hypoglycemic drugs were tapered or the treatments discontinued as needed (Table 1).

Recombinant leptin was administered subcutaneously every 12 hours. The physiologic replacement dose was estimated to be 0.03 mg per kilogram of body weight per day for girls under 18 years of age and 0.04 mg per kilogram per day for women on the basis of information provided by the manufacturer. These doses are approximately 1/10 of the dose most commonly used in obesity trials. Patients were treated with 50 percent of the replacement dose for the first month, 100 percent for the second month, and 200 percent for the third and fourth months.

Biochemical Analyses

Serum glucose and triglyceride levels were determined according to standard methods with the use of automated equipment (Hitachi, Boehringer Mannheim, Indianapolis) at the NIH and a Beckman instrument (Fullerton, Calif.) at the University of Texas

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS AND TREATMENT REGIMENS AT BASE LINE AND AFTER FOUR MONTHS OF RECOMBINANT LEPTIN.

PATIENT No.	AGE (YR)/SEX	TYPE OF LIPODYSTROPHY	FASTING INSULIN*	LEPTIN†	RESTING METABOLIC RATE	TOTAL FAT‡	LIPID-LOWERING THERAPY AT BASE LINE	THERAPY FOR HYPOGLYCEMIA	
			$\mu\text{U/ml}$	ng/ml	kcal/day	%		AT BASE LINE	AT 4 MO
1	17/F	Acquired, generalized	31	<0.5	2010	7	Fenofibrate, atorvastatin, orlistat, weekly plasmapheresis	Metformin (500 mg twice daily), acarbose (50 mg 3 times daily)	None
2	17/F	Congenital, generalized	334	1.0	2030	17	None	Insulin (800 U/day)	None
3	27/F	Acquired, generalized	19	0.7	1570	18	None	Insulin (40 U/day), metformin (500 mg 3 times daily)	Metformin (500 mg twice daily)
4	17/F	Congenital, generalized	211	1.1	2480	17	None	Insulin (1200 U/day)	None
5	15/F	Congenital, generalized	115	0.8	2670	15	None	Insulin (3000 U/day)	None
6	37/F	Congenital, generalized	25	0.6	1370	15	None	Metformin (500 mg 3 times daily)	None
7	42/F	Familial, partial	40	3.6	1980	26	Gemfibrozil	Insulin (200 U/day), pioglitazone (45 mg/day)	Insulin (60 U/day)
8	31/F	Congenital, generalized	62	0.7	1702	8	Fenofibrate	Insulin (700 U/day)	Insulin (300 U/day)
9§	33/F	Acquired, generalized	12	2.4	1497	14	Gemfibrozil	None	None

*To convert values for insulin to picomoles per liter, multiply by 7.15. The normal range is 5 to 15 μU per milliliter (36 to 107 pmol per liter). Some patients were receiving insulin therapy.

†To convert values for leptin to nanomoles per milliliter, multiply by 0.08. Levels of less than 4.0 ng per milliliter (0.32 nmol per milliliter) are below the 5th percentile of values for the general population in the United States.¹²

‡Total fat was measured by dual-energy x-ray absorptiometry, which yields values that are 7 to 8 percent higher than those obtained with use of an underwater-weighing technique.

§Patient 9 did not have diabetes.

Southwestern Medical Center. Glycosylated hemoglobin values were measured by ion-exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, Calif.), and levels of free fatty acids were measured with use of a commercial kit (Wako, Richmond, Va.). Serum insulin levels were determined by immunoassays with the use of reagents provided by Abbott Instruments (Abbott Park, Ill.) at the NIH and a commercial kit (Linco Research, St. Charles, Mo.) at the University of Texas Southwestern Medical Center. Serum leptin levels were determined by immunoassays with the use of a commercial kit (Linco Research).

Procedures

The resting metabolic rate was measured (Deltatrac equipment, Sensormedics, Yorba Linda, Calif.) between 6 a.m. and 8 a.m. while patients rested, after an overnight fast of more than eight hours. After an overnight fast, each patient underwent an oral glucose-tolerance test in which 75 g of dextrose was administered orally.

A high-dose insulin-tolerance test was performed with the use of 0.2 U of regular insulin per kilogram to assess the patients' sensitivity to insulin. The K constant (the rate of glucose disappearance as a reflection of the body's overall sensitivity to insulin) was calculated as the rate constant for the decrease in blood glucose levels after the intravenous administration of insulin with the use of first-order kinetics.¹⁷ The seven patients who were seen at the NIH Clinical Center reported their daily food intake at base line and at four months using a standardized questionnaire.¹⁸

Body fat was determined with use of a dual-energy x-ray absorptiometer (model QDR 4500, Hologic, Bedford, Mass.).¹⁹ Axial T₁-weighted magnetic resonance imaging of the liver was performed with use of a 1.5-T scanner (General Electric Medical Systems, Milwaukee, at the NIH and Philips Medical Systems, Best, the Neth-

erlands, at the University of Texas Southwestern Medical Center).²⁰ Liver volumes were calculated with use of the MEDx image-analysis software package (Sensor Systems, Sterling, Va.).

Statistical Analysis

Values are presented as means ±SE. We used an analysis of variance with repeated measures to compare the study variables during various study periods. Skewed data on triglyceride levels and calculated K constants were log-transformed. We used a paired t-test wherever it was applicable to compare base-line data with data obtained at various times. We analyzed changes in plasma glucose levels during the oral glucose-tolerance test using a two-factor analysis of variance in which the study period and the time during the test were modeled as repeated factors. We calculated 95 percent confidence intervals for the differences between the means according to the method of Hahn and Meeker.²¹ The manuscript was jointly written by a committee of the investigators.

RESULTS

Base-Line Characteristics of the Patients

Eight of the nine patients in the study had diabetes (Table 1), and all nine had hyperlipidemia (Table 2). All patients with diabetes were receiving medications for their diabetes before the study began, and four of the nine patients received lipid-lowering therapy (Table 1). Their average glycosylated hemoglobin value was 9.1±0.5 percent (normal, less than 5.6 percent) at the base-line evaluation. The mean triglyceride levels were elevated at base line, at 1405 mg per deciliter (16

TABLE 2. METABOLIC VALUES BEFORE AND DURING TREATMENT WITH RECOMBINANT LEPTIN.*

PATIENT NO.	FASTING PLASMA GLUCOSE†					GLYCOSYLATED HEMOGLOBIN					FASTING PLASMA TRIGLYCERIDES‡				
	PRE	0	1	2	4	PRE	0	1	2	4	PRE	0	1	2	4
	mg/dl					%					mg/dl				
1	243	266	218	187	128	8.3	8.6	7.6	7.4	7.0	9560	7420	6440	1632	1214
2§	251	194	121	106	166	10.0	9.8	8.3	7.4	10.0	650	633	523	471	405
3	262	223	234	171	135	9.1	9.3	7.8	8.4	7.9	559	450	579	233	281
4	165	138	145	93	71	7.8	7.6	6.7	6.1	5.0	445	322	232	160	106
5	246	207	207	91	107	9.8	9.5	9.4	6.5	6.1	789	913	427	143	123
6	333	301	108	70	225	10.6	9.2	8.6	7.2	7.4	703	663	355	242	303
7	295	321	228	204	162	9.1	9.5	8.4	7.4	6.6	921	802	366	295	215
8	187	219	114	99	105	10.2	9.5	8.1	7.5	7.3	1456	995	827	383	192
9¶	84	90	84	79	89	4.9	5.4	4.8	5.0	5.1	1114	447	656	276	424

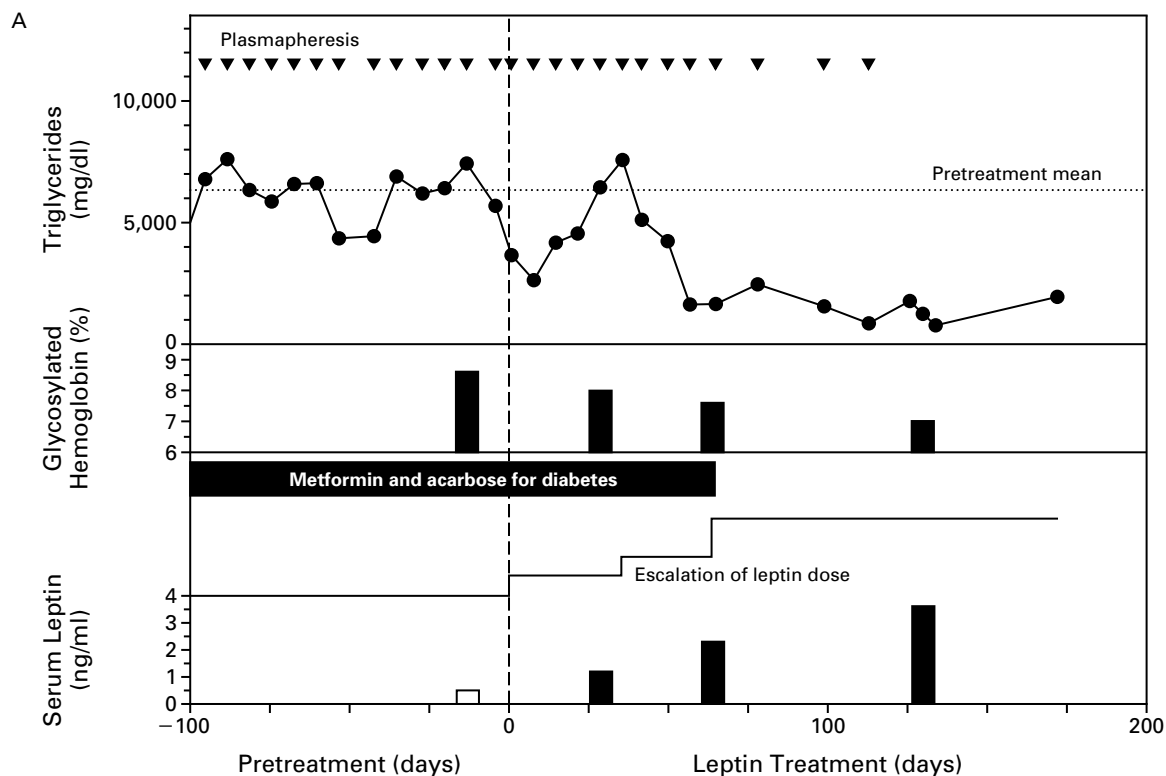
*Pretreatment (Pre) values were collected six weeks to eight months before the trial began, while the patients were receiving the therapies shown in Table 1. Month 0 refers to the base-line evaluation period.

†To convert values for fasting plasma glucose to millimoles per liter, multiply by 0.0551. The normal range is 75 to 110 mg per deciliter (4.1 to 6.1 mmol per liter).

‡To convert values for fasting plasma triglycerides to millimoles per liter, multiply by 0.01129. The normal range is 35 to 155 mg per deciliter (0.4 to 1.7 mmol per liter).

§Patient 2 was noncompliant during the third and fourth months of therapy. After an initial two months of strict compliance, as documented by a count of the vials of medication used, the reported values were as follows: fasting plasma glucose, 109 mg per deciliter (6.0 mmol per liter); glycosylated hemoglobin, 7.3 percent; and fasting plasma triglycerides, 283 mg per deciliter (3.2 mmol per liter).

¶Patient 9 did not have diabetes.



B

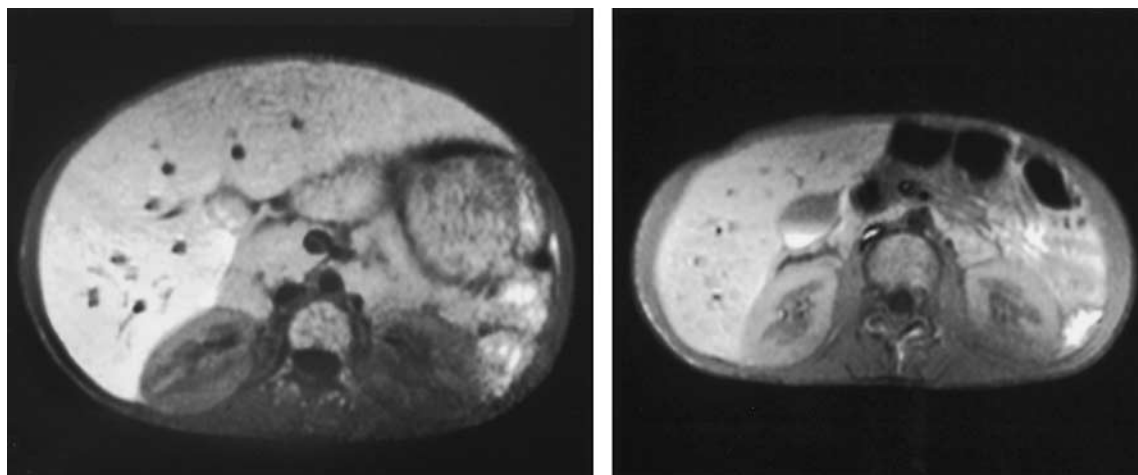


Figure 1. Clinical Course of Patient 1, as Assessed by Changes in Mean Triglyceride Levels, Glycosylated Hemoglobin Values, and Serum Leptin Values.

Patient 1 was healthy at birth but began to lose fat between the ages of 10 and 12 years. Severe hypertriglyceridemia developed at the age of 13 years, and diabetes at the age of 14 years. When she presented to the NIH Clinical Center at the age of 15 years, her triglyceride levels consistently exceeded 10,000 mg per deciliter (113 mmol per liter) and her glycosylated hemoglobin value was 9.5 percent. She had painful eruptive cutaneous xanthomata all over her body and massive hepatomegaly, extending to the pelvic brim. Weekly plasmapheresis therapy and orlistat were added to alleviate hypertriglyceridemia (Panel A).²² Over a four-month period, treatment with recombinant leptin caused a marked, progressive improvement in hypertriglyceridemia and hyperglycemia that allowed plasmapheresis and medications for diabetes to be discontinued. The improvements in metabolic values were accompanied by the disappearance of cutaneous xanthomata. In addition, the liver volume decreased by nearly 40 percent, from 4213 ml to 2644 ml (Panel B; both scans are at the same level and scale). To convert triglyceride values to millimoles per liter, multiply by 0.01129. To convert leptin values to nanomoles per milliliter, multiply by 0.08.

mmol per liter) (range, 322 to 7420 mg per deciliter [3.6 to 83.8 mmol per liter]; normal range, 35 to 155 mg per deciliter [0.4 to 1.7 mmol per liter]). Free fatty acid levels were also increased, at a mean of 1540 ± 407 μmol per liter (normal, 350 to 550).

Changes in Circulating Leptin Levels

The mean serum leptin level was 1.3 ± 0.3 ng per milliliter (0.1 ± 0.02 nmol per milliliter) at base line (Table 1) and increased to 2.3 ± 0.5 ng per milliliter (0.2 ± 0.04 nmol per milliliter) at the end of the first month of therapy, to 5.5 ± 1.2 ng per milliliter (0.4 ± 0.1 nmol per milliliter) at the end of the second month, and to 11.1 ± 2.5 ng per milliliter (0.9 ± 0.2 nmol per milliliter) at the end of the fourth month. Thus, the administration of recombinant leptin resulted in approximately normal serum leptin levels in these patients.¹²

Changes in Metabolic Control

The first patient treated in this study (Patient 1) was also the most severely affected,²² and her clinical course is shown in Figure 1. Leptin-replacement therapy had a marked effect in this patient and in the group as a whole.²² Before the initiation of leptin therapy, the eight patients with diabetes had poor metabolic control, with a mean glycosylated hemoglobin value of 9.1 ± 0.5 percent. After four months of leptin-replacement therapy, the glycosylated hemoglobin value decreased by a mean of 1.9 percentage points (95 percent confidence interval, 1.1 to 2.7; $P=0.001$). The individual responses of the patients are provided in Table 2. Glycemic control improved despite the fact that antidiabetic therapy was decreased or discontinued during the four months of leptin-replacement therapy (Table 1).

At the end of four months of recombinant leptin therapy, the fasting triglyceride levels had fallen by 60 percent (95 percent confidence interval, 43 to 77 percent; $P<0.001$). The individual responses of the patients are given in Table 2. During the same period, fasting levels of free fatty acids fell from a mean of 1540 ± 407 μmol per liter to 790 ± 164 μmol per liter ($P=0.05$).

The insulin-tolerance test showed that plasma glucose levels had significantly decreased at the end of four months of therapy (Fig. 2A). The K constant (the rate of glucose disappearance) increased from 0.007 ± 0.001 to 0.017 ± 0.004 , indicating an improvement in whole-body sensitivity to insulin ($P=0.04$). Furthermore, the glucose levels measured in response to an oral glucose load (75 g of dextrose) were significantly lower than the base-line levels (Fig. 2B).

Since all patients derived clinically significant benefit from leptin-replacement therapy, all continue to receive treatment.

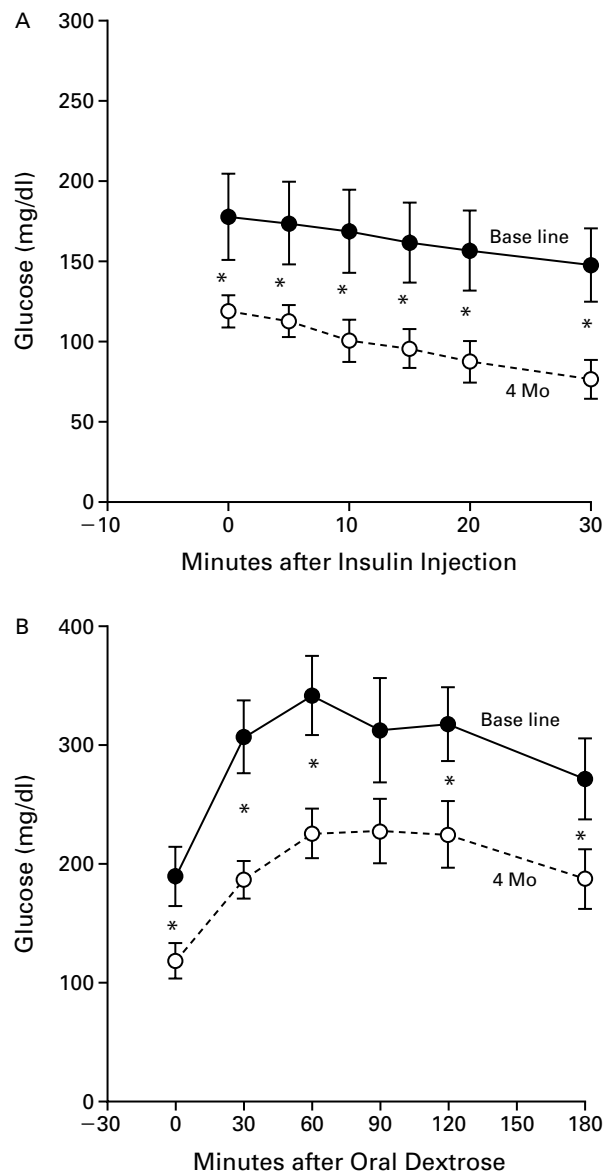


Figure 2. Mean (\pm SE) Plasma Glucose Levels in Response to an Insulin-Tolerance Test (Panel A) and an Oral Glucose-Tolerance Test (Panel B) in Nine Patients at Base Line and after Four Months of Leptin-Replacement Therapy.

Leptin improved the glucose curves during both the insulin-tolerance test and the oral glucose-tolerance test. In Panel A, plasma glucose levels were measured before and after the intravenous administration of 0.2 U of insulin per kilogram before and after four months of leptin-replacement therapy. Asterisks indicate a significant difference ($P<0.02$) between groups. In Panel B, plasma glucose levels were measured during an oral glucose-tolerance test with 75 g of dextrose before and after four months of leptin-replacement therapy. Asterisks indicate a significant difference ($P<0.01$) between groups. To convert glucose values to millimoles per liter, multiply by 0.0551.

Changes in Liver Volume and Liver-Function Tests

At base line, the mean liver volume was 3097 ± 391 ml (approximately four times the volume in age- and sex-matched persons of normal weight). Leptin decreased the liver volume by an average of 28 percent (95 percent confidence interval, 20 to 36 percent) from base line ($P=0.002$). The decrease in liver size was associated with an improvement in liver-function tests. Base-line alanine aminotransferase levels had decreased from 66 ± 16 to 24 ± 4 U per liter at the end of four months of therapy ($P=0.02$). Likewise, serum aspartate aminotransferase levels were 53 ± 12 U per liter at base line and 21 ± 2 U per liter at the end of four months of therapy ($P=0.03$).

Changes in Energy Balance

Data on self-reported daily caloric intake were available for seven patients. The daily caloric intake decreased from a mean of 2680 ± 250 kcal per day at base line to 1600 ± 150 kcal per day after four months of leptin-replacement therapy ($P=0.005$). There was a parallel decrease in the resting metabolic rate (measured in all nine patients), from 1920 ± 150 to 1580 ± 80 kcal per day ($P=0.003$).

All but one patient (Patient 3) had lost weight at the end of four months of treatment (mean weight loss, 3.6 ± 0.9 kg; range, -1.7 to 7.3). An important fraction of the weight loss (50 to 65 percent) was attributed to the decrease in liver volume.

Adverse Events

Patient 1 had a severe episode of nausea and vomiting after the first dose of recombinant leptin. After the second dose, Patient 6 had an exacerbation of hypertension associated with flushing. Patient 7 was hospitalized for a streptococcal infection during the third month of therapy. All these events resolved, and none recurred with the continuation of therapy. No skin reactions at injection sites were reported or observed.

Withdrawal of Recombinant Leptin

Since the patients had reduced their intake of food during leptin-replacement therapy, we assessed whether the metabolic values were maintained in the presence of a reduced intake of food. Patient 1 was admitted to the NIH Clinical Center and received 1900 kcal per day (55 percent carbohydrates, 25 percent fat, and 20 percent protein), which was based on the patient's reported intake of food during leptin-replacement therapy and on a measurement of the resting metabolic rate, in the form of three meals and two snacks. Leptin-replacement therapy was stopped after day 5. Plasma glucose levels were measured before each meal and at bedtime, and the daily averages were calculated. Fasting plasma triglyceride and insulin levels were determined. Within 48 hours after the with-

drawal of recombinant leptin, the fasting plasma triglyceride and insulin levels began to increase. The effects were corrected by the resumption of leptin-replacement therapy (Fig. 3).

DISCUSSION

Leptin-replacement therapy led to clear and dramatic metabolic benefits in this group of nine patients with lipodystrophy and leptin deficiency. Treatment with recombinant leptin resulted in an absolute reduction in the glycosylated hemoglobin value of 1.9 percent. Such a reduction is predicted to decrease the relative risk of retinopathy by approximately 48 percent and nephropathy by approximately 22 percent in the diabetic population.²³ Furthermore, triglyceride levels fell by 60 percent, and such a reduction is predicted to decrease the relative risk of cardiovascular events in the general population by 35 to 65 percent.^{24,25}

To date, the insulin resistance and hypertriglyceridemia that characterize lipodystrophy have been refractory to treatment.²⁶ Thiazolidinediones appear to be the most effective therapy, albeit an imperfect one.²⁷ Commonly, this condition is managed with a combination of medications, including high doses of insulin, oral hypoglycemic agents (e.g., metformin and thiazolidinediones), and lipid-lowering drugs (e.g., fibrates and statins). Despite such therapy, patients continue to have severe hypertriglyceridemia, leading to recurrent attacks of acute pancreatitis; severe hyperglycemia, posing risks of diabetic retinopathy and nephropathy; and nonalcoholic steatohepatitis, which can result in cirrhosis. Leptin-replacement therapy appears to have the potential to prevent all these complications.

Our results also demonstrate a novel action of leptin. Leptin appears to provide a signal that regulates total-body sensitivity to insulin and triglyceride levels in addition to its known role in the control of energy homeostasis.

Although our study was not randomized, the improved metabolic control appeared to be due to leptin-replacement therapy rather than to an improvement in general compliance associated with participation in a study.

An important unanswered question is the effect of decreased food intake on the changes in metabolic values in this study. In patients with lipodystrophy, limiting caloric intake improves glucose and lipid abnormalities.²⁸ Leptin-replacement therapy reduced food intake in our patients. However, in an analysis involving Patient 1, we observed an additional effect of leptin-replacement therapy on insulin sensitivity and triglyceride metabolism that was independent of food intake. In this patient, fasting insulin and triglyceride levels increased within two and four days,

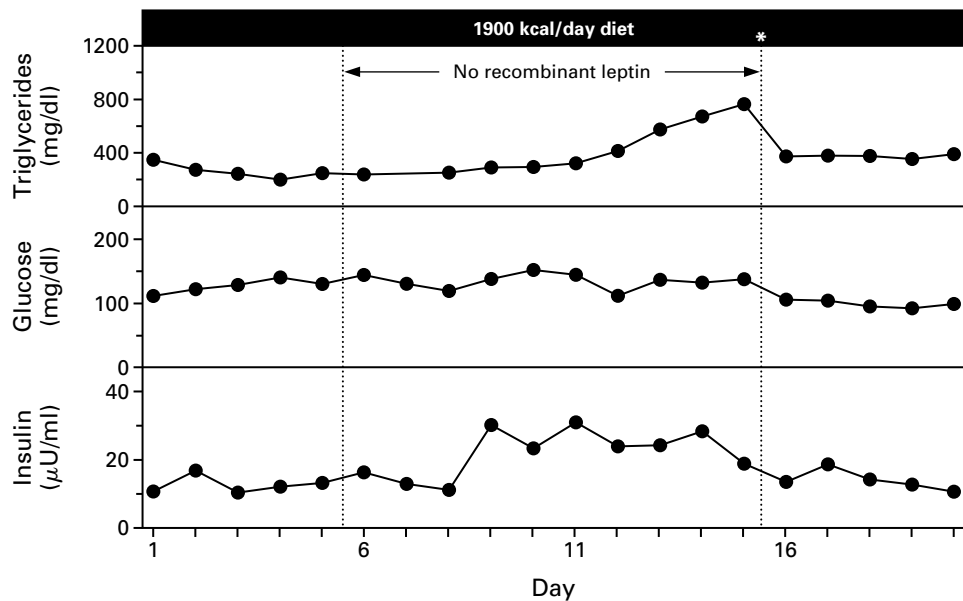


Figure 3. Effects of Leptin-Replacement Therapy on Insulin Sensitivity and Triglyceride Levels in Patient 1 while She Was Following a Diet Containing 1900 kcal per Day.

The effects of leptin-replacement therapy appeared to be independent of the decrease in food intake. Patient 1 was hospitalized and given a diet containing 1900 kcal per day (according to the estimated intake of food while she was receiving 0.08 mg of recombinant leptin per kilogram per day). Recombinant leptin was withdrawn at the end of day 5 while all other medications were kept constant. Fasting plasma insulin levels (normal range, 5 to 15 μU per milliliter [36 to 107 pmol per liter]), fasting plasma triglyceride levels (normal range, 35 to 155 mg per deciliter [0.4 to 1.7 mmol per liter]), and mean daily glucose levels are shown. Leptin-replacement therapy was resumed on day 15, when nausea, vomiting, and abdominal pain developed consistent with the presence of pancreatitis. The asterisk refers to the 24-hour period of pancreatitis during which there was no oral intake. To convert triglyceride values to millimoles per liter, multiply by 0.01129. To convert glucose values to millimoles per liter, multiply by 0.0551. To convert insulin values to picomoles per liter, multiply by 7.15.

respectively, after recombinant leptin was withdrawn even though the level of food intake remained constant. Similar data have been reported in paired-feeding experiments (with or without leptin administration) involving lipoatrophic mice.^{10,29}

Leptin has been identified as the missing hormone in obese (*ob/ob*) mice.¹ In these mice, leptin-replacement therapy decreased food intake and body weight.³⁰⁻³² Because of such initial observations, obesity has been the focus of most therapeutic trials with leptin. However, most obese people have high serum leptin levels and are therefore presumed to have leptin resistance.³³ Thus far, the average weight loss in obese persons has not been significant,³⁴ except in patients with congenital leptin deficiency.⁵

Study of various mouse models of lipodystrophy suggests that the absence of adipose tissue is the cause of insulin resistance in this syndrome.³⁵⁻³⁷ The demonstration that transplantation of adipose tissue into mice with lipodystrophy ameliorates insulin resistance and improves metabolic control provides

strong support for this hypothesis.⁹ However, why adipose tissue was required to maintain whole-body sensitivity to insulin has remained unclear. Shimomura et al. tested the efficacy of leptin replacement in a mouse model and observed a dramatic improvement in glucose and triglyceride levels and hepatic steatosis.¹⁰ Taken together, these observations and our results suggest that leptin controls the majority of the regulatory action of adipose tissue on whole-body sensitivity to insulin.

In our study, leptin-replacement therapy was associated with a decline in the resting metabolic rate. This finding is parallel to observations in patients with a congenital absence of leptin.³³ Although the mechanism of this effect is unclear, we presume that the leptin-induced decrease in food intake reduces diet-induced thermogenesis.

Unger and colleagues have reported that leptin administration in Zucker rats corrects steatosis in a variety of organs that act as sites of lipid accumulation, such as the liver, islet cells, and the heart.^{38,39}

The accumulation of lipids at these sites may represent a spillover phenomenon resulting from the fact that adipocytes have reached their capacity to store triglycerides. In patients with lipodystrophy, these organs are the only sites that can store lipids. Leptin treatment of mice with lipodystrophy causes a dramatic decrease in hepatic stores of triglycerides. In parallel, leptin-replacement therapy in our patients with lipodystrophy caused a significant reduction in liver volume.

The concept that adipose tissue is an endocrine organ was strongly supported by the discovery of leptin. Leptin has effects (direct or indirect) on the key organs of metabolism, including the brain, liver, muscle, fat, and pancreas. Leptin is certainly not the only circulating adipocyte signal.⁴⁰⁻⁴² Lack of adipocytes should result in a deficiency of all fat-derived signals. On the basis of our findings, leptin deficiency appears to be the chief contributor to the metabolic abnormalities associated with lipodystrophy. Thus, severe lipodystrophy may be an important reason to consider leptin-replacement therapy. The optimal dose of recombinant leptin in patients with lipodystrophy, the role of leptin-replacement therapy in treating other insulin-resistance states, and the degree of leptin deficiency that will respond to leptin-replacement therapy remain to be determined.

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