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Long-term efficacy of leptin replacement in patients with Dunnigan-type familial partial lipodystrophy

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Abstract

The Dunnigan-type familial partial lipodystrophy (FPLD) is characterized by a variable loss of fat from the extremities and trunk and excess subcutaneous fat in the chin and supraclavicular area. Associated metabolic abnormalities include hypoleptinemia, insulin resistance, and dyslipidemia. Our goal was to observe changes in metabolic parameters for patients with FPLD on long-term leptin replacement and to compare the metabolic characteristics seen in FPLD with those seen in generalized lipodystrophy (GL) from our previous studies. This was an open-label study of 6 patients with FPLD receiving maximal doses of oral antidiabetic and lipid-lowering medications at baseline. Recombinant leptin was given through twice-daily subcutaneous injections at a maximal dose of 0.08 mg/kg per day over 12 months to simulate normal to high normal physiologic levels. Triglycerides were reduced by 65% at 4 months (749 ± 331 to 260 ± 58 mg/dL) and significantly reduced at 12 months for 5 patients (433 ± 125 to 247 ± 69 mg/dL; $P = .03$). Total cholesterol also decreased (280 ± 49 to 231 ± 41 mg/dL; $P = .01$). Insulin sensitivity and fasting glucose levels (190 ± 26 to 151 ± 15 mg/dL; $P < .01$) improved. Glucose tolerance and glycosylated hemoglobin levels (8.4% ± 0.6% to 8.0% ± 0.4%; $P = .07$) did not change. As shown in patients with GL, patients with FPLD have improvement in triglycerides, fasting glucose, and insulin sensitivity with leptin replacement. In contrast to the patients with GL, the patients with FPLD are older, have higher leptin levels, and notably lower insulin secretion for a similar degree of hyperglycemia. Low-dose recombinant methionyl human leptin for patients with FPLD has an important role in improving triglycerides, beyond that of available lipid-lowering agents. In improving glycemic control, normalization of glucose tolerance in hypoinsulinemic patients with FPLD requires insulin and leptin therapy. This is the first study to examine the effects of long-term leptin replacement in patients with FPLD.

1. Introduction

Leptin was discovered as the protein product lacking as a result of the mutated gene in the obese (*ob/ob*) mouse [1]. Because leptin administration to the *ob/ob* mouse corrected obesity and other metabolic disorders [2-4], leptin was given to obese humans in an attempt to reduce body weight. Because circulating leptin concentrations are primarily a function of the adipocyte mass, these patients had high circulating leptin concentrations and had only a limited response to exogenous leptin administration [5]. Thus, hyperleptinemic states are resistant to exogenous leptin therapy.

Lipodystrophy is a clinical state in rodents and humans in which serum leptin levels are low. Leptin-deficient rodents have been shown to be responsive to exogenous leptin administration [6]. This is true as well in humans with congenital leptin-deficient states [7-9] and in congenital and acquired forms of lipodystrophy [10,11].

Generalized forms of lipodystrophy are characterized by very low serum leptin concentrations, insulin resistance, dyslipidemia, diabetes mellitus, and nonalcoholic steatohepatitis (NASH). Recombinant leptin administration ameliorates these abnormalities [10-12].

Partial forms of lipodystrophy share these metabolic abnormalities, but because the adipocyte mass is greater in these patients, the circulating leptin levels are proportionately higher [13]. The Dunnigan-type familial partial lipodystrophy (FPLD) is due to mutations in the encoding lamin A/C (*LMNA*) gene [14]. FPLD is characterized by a

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loss of subcutaneous tissue from the extremities and trunk, with abnormal accumulation in the supraclavicular area and chin [15]. Patients have variable serum leptin levels and similar metabolic abnormalities as in generalized lipodystrophy (GL) [16,17]. In this small study, we investigated the role of low-dose recombinant leptin therapy in patients with FPLD to determine (1) the response of metabolic parameters to treatment, (2) the safety and tolerability of treatment over the long term, and (3) the differences of metabolic parameters at baseline and in response to treatment in patients with FPLD and GL.

2. Research design and methods

2.1. Subject population and study design

We evaluated 6 female patients with FPLD between 2000 and 2004. Patients with FPLD have mutations in the *LMNA* gene and can be referred to as Dunnigan-type FPLD, type 2 (FPLD2) [14]. Five of the 6 patients evaluated had the R482Q alteration in exon 8 of the *LMNA* gene and were reported previously [18]. This mutation was first described when the candidate gene for FPLD, *LMNA*, was described [19]. The remaining patient (NIH-7) has the R482W mutation in exon 8 (Abhimanyu Garg, personal communication, May 2006). Inclusion criteria for recombinant methionyl human leptin (r-metHuLeptin) therapy included relative hypoleptinemia (serum leptin <5 ng/mL), metabolic abnormalities such as hypertriglyceridemia (>200 mg/dL), hyperinsulinemia (>30 μU/mL), and diabetes, and ability to adhere to leptin therapy and the protocol regimen. These 6 patients met the inclusion criteria to initiate therapy with r-metHuLeptin. NIH-12 and NIH-17 are sisters, and NIH-23 is their cousin. One patient was presented in the initial 4-month study [10].

The comparison group, patients with GL secondary to either congenital GL or acquired GL, were evaluated and reported previously [11].

R-metHuLeptin therapy was given as a self-administered, twice-daily subcutaneous injection as previously described [10]. The dose was escalated to the full dose over the first 2 months of treatment. Thereafter, the usual replacement dose was 0.08 mg/kg per day in an attempt to simulate the normal to high physiologic range. Patients were evaluated at the Clinical Research Center of the National Institutes of Health at baseline, every 4 months for 1 year, and every 6 months thereafter. Inpatient data were collected on a metabolic unit during each visit. At baseline, patients were on oral antidiabetic medications for diabetes and dyslipidemia. Medications were not added or increased during the first year of study. One patient was on insulin therapy before the study. Insulin therapy was not initiated for all the other patients during the first year of the study. Results were analyzed as a function of baseline. The protocol was approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. Informed consent was obtained from each patient.

Data for the first 12 months of the study are presented for all 6 patients with FPLD, although we realized at the end of the 12 months that 2 patients were intermittently noncompliant in the administration of r-metHuLeptin, not related to any side effects of the treatment. These patients (NIH-18 and NIH-21) were withdrawn from the study at 12 months, and the remaining patients were followed up for an additional 2 to 4 years.

Data from the first 12 months of treatment of the patients with GL were reported in 15 patients. Twenty patients met the inclusion criteria, and 5 patients were withdrawn from r-metHuLeptin therapy before 12 months [11].

2.2. Biochemical analyses

Serum leptin levels were determined by immunoassays with the use of a commercial kit (Linco Research, St Charles, MO). Glycosylated hemoglobin (HbA_{1c}) values were measured by ion exchange high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA). Serum thyroid-stimulating hormone (TSH), growth hormone (GH), insulinlike growth factor 1 (IGF-1), and C-reactive protein (CRP) levels were measured with a 2-site chemiluminescent immunometric assay on DPC Immulite 2000 equipment (Diagnostic Products, Los Angeles, CA). Free thyroxine (FT_4) was measured with an electrochemiluminescent competitive immunoassay on Elecsys 2010 equipment (Roche Diagnostics, Indianapolis, IN). Insulin was determined by immunoassay (Abbott Imx Instrument, Abbott Park, IL). Serum glucose and lipid values were determined according to standard methods with the use of

Table 1
Baseline clinical characteristics of patients

Patient No.[a]	Age/Sex y (M/F)	Serum leptin[b] (ng/mL)	Weight (kg)	BMI (kg/m^2)	Body fat (%)	REE (kJ/24 h)
NIH-7	42/F	2.5	64.7	24.6	13.7	8284
NIH-12	64/F	3.5	54.7	21.9	27.3	4477
NIH-17	44/F	4.5	56.4	23.1	22.2	5690
NIH-18	51/F	4.5	64.4	24.8	22.2	ND
NIH-21	33/F	3.9	58.2	20.2	19.8	5146
NIH-23	43/F	3.9	74.0	25.3	24.4	5523
Mean ± SEM	46 ± 4.3	3.8 ± 0.3	62.1 ± 2.9	23.3 ± 0.8	21.6 ± 1.9	5824 ± 649

[a] NIH numbers correspond to previous publications.
[b] Normal fasting range of leptin for men, 3.8 ± 1.8 ng/mL; women, 7.4 ± 3.7 ng/mL [36].

Table 2
Baseline laboratory parameters of patients

Patient No.	Fasting glucose (mg/dL)	HbA_{1c} (%)	Triglycerides (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	Total cholesterol (mg/dL)	GH (ng/mL)	IGF-1 (ng/mL)	TSH μIU/mL	FT_4 (ng/dL)	CRP (mg/dL)	Liver volume (cm^3)
NIH-7	267[a]	9.5	802	30	136	245	0.1	45	0.63	0.8	0.40	3135
NIH-12	181[a]	9.0	198	51	148	225	0.2	200	2.57	1.0	0.40	1274
NIH-17	259[a]	9.7	550	36	132	231	0.3	75	1.62	0.9	0.48	2068
NIH-18	164[b]	7.8	503	36	122	242	2.9	146	0.79	0.9	0.40	1930
NIH-21	94[b]	5.7	2324	40	[c]	524	0.1	112	0.34	1.1	8.96	2045
NIH-23	179[a]	8.6	114	44	135	210	0.1	69	1.68	1.2	0.40	2378
Mean ± SEM	190 ± 26	8.4 ± 0.6	749 ± 331	40 ± 3	135 ± 4	280 ± 49	0.6 ± 0.5	108 ± 23	1.27 ± 0.34	1.0 ± 0.1	0.42 ± 0.02[d]	2138 ± 249

[a] Single fasting glucose obtained before r-metHuLeptin therapy; each patient's antidiabetic medications are shown in Table 4.
[b] Single fasting glucose obtained before r-metHuLeptin therapy; NIH-18 was on metformin and rosiglitazone and NIH-21 was on pioglitazone.
[c] Lipemic sample did not have direct LDL assay.
[d] NIH-21 not included in mean ± SEM; CRP elevated from pancreatitis.

automated equipment (Beckman, Fullerton, CA). All values represent morning fasting levels.

2.3. Procedures

To assess changes in energy and macronutrient intake, subjects completed the Block 1998 Revision of the Health Habits and History Questionnaire, a self-administered standardized semiquantitative food frequency questionnaire, at baseline and each subsequent visit to reflect intake between visits [20]. Resting energy expenditure (REE) (Deltatrac equipment, Sensormedics, Yorba Linda, CA) was measured between 6:00 AM and 8:00 AM after an overnight fast of at least 8 hours, while the patients remained at rest. After an overnight fast, each patient underwent an oral glucose tolerance test (OGTT) in which 1.75 up to 75 g/kg of dextrose was administered. A high-dose insulin tolerance test was performed with the use of 0.2 U of regular insulin per kilogram administered intravenously to assess the patients' sensitivity to insulin. Percent body fat was determined by dual-energy x-ray absorptiometry (QDR 4500, Hologic, Bedford, MA). Axial T1-weighted magnetic resonance imaging of the patients' livers was performed with the use of a 1.5-T scanner (General Electric Medical Systems, Milwaukee, WI). The liver volumes were estimated with the use of MEDx image-analysis software package (Sensor Systems, Sterling, VA).

2.4. Statistical analyses

Values are expressed as mean ± SE. SigmaStat (SPSS, Chicago, IL) was used to calculate a 1-way analysis of variance for repeated measures. Unpaired *t* tests were used when applicable for comparing data between patients with

Table 3
Physical and biochemical changes during leptin

Test	Baseline	4 mo	8 mo	12 mo	*P*
Leptin[a] (ng/mL)	3.8 ± 0.3	25.5 ± 5.2	23.1 ± 5.7	37.4 ± 15.6	.038
Fasting glucose (70-99 mg/dL)	190 ± 26	140 ± 18**	138 ± 11	151 ± 15	.006
HbA_{1c} (4.8%-6.4%)	8.4 ± 0.6	7.3 ± 0.5*	7.9 ± 0.4	8.0 ± 0.4	.069
Triglycerides (<150 mg/dL)	749 ± 331	260 ± 58	342 ± 99	510 ± 269	.097†
HDL (mg/dL)	40 ± 3	36 ± 3	39 ± 3	36 ± 5	.468
LDL (65-99 mg/dL)	135 ± 4	132 ± 8	121 ± 8	118 ±8	.052
Total cholesterol (100-200 mg/dL)	280 ± 49	201 ± 4	232 ± 31	231 ± 41	.012
Fasting GH (0.0-10.0 ng/mL)	0.6 ± 0.5	0.8 ± 0.3	0.5 ± 0.2	0.8 ± 0.4	.801
IGF-1 (182-780 ng/mL)	108 ± 23	139 ± 33	106 ± 41	103 ± 22	.043
CRP (<0.80 mg/dL)	0.42 ± 0.02[b]	0.40 ± 0.00	0.50 ± 0.04	0.46 ± 0.04	.364
TSH (0.4-4.0 μIU/mL)	1.27 ± 0.34	1.42 ± 0.45	1.51 ± 0.57	1.69 ± 0.56	.456
FT_4 (0.8-1.9 ng/dL)	1.0 ± 0.1	1.1 ± 0.2	1.0 ± 0.1	1.1 ± 0.1	.069
Liver volume (cm^3)	2138 ± 249	1898 ± 242	1938 ± 172	1967 ± 262	.055
Weight (kg)	62.1 ± 2.9	59.3 ± 2.8	59.6 ± 3.2	60.2 ± 2.6	.032
BMI (kg/m^2)	23.3 ± 0.8	22.3 ± 0.7	22.7 ± 0.5	22.7 ± 0.5	.024
Body fat (%)	21.6 ± 1.9	20.2 ± 1.8	20.1 ± 1.5	20.2 ± 1.6	.069
Energy expenditure (kJ/24 h)	5096 ± 649	5620 ± 411	5189 ± 921	5096 ± 451	.761

[a] Samples were taken after an overnight fast and ~8 to 10 hours after the last r-metHuLeptin injection.
[b] NIH-21 is excluded; CRP levels at baseline were elevated because of pancreatitis.
* $P < .05$ compared with baseline.
** $P = .01$ compared with baseline.
† $P = .026$, when NIH-21 is excluded.

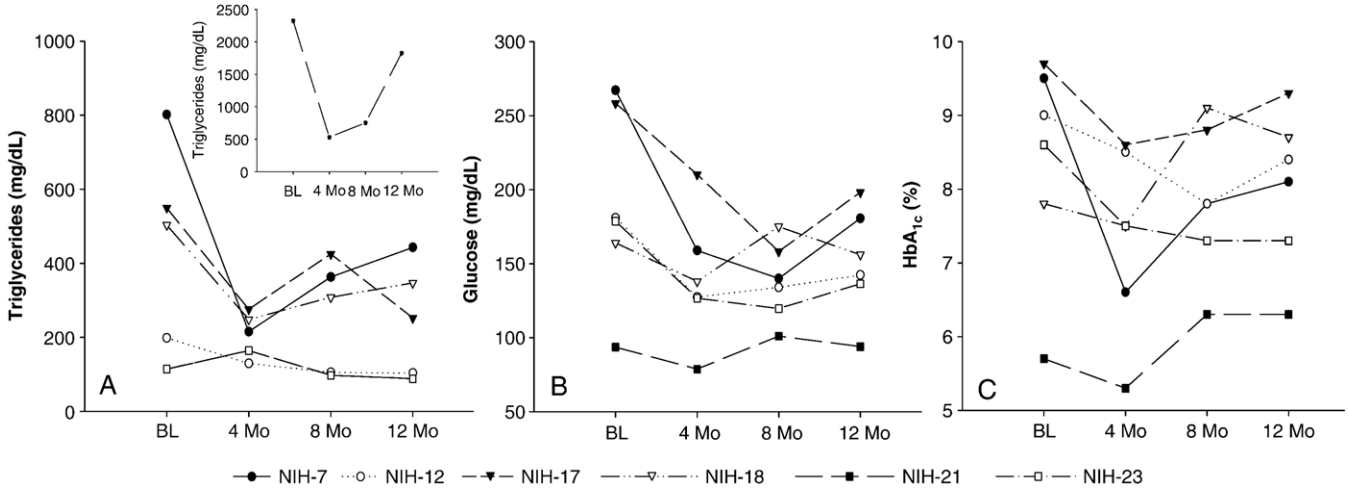

Fig. 1. Triglycerides, fasting glucose and HbA_{1c} results of each of the patients while on r-metHuLeptin replacement for 12 months. A, NIH-21 has a significant decrease in triglycerides at 4 months, but increased (likely due to noncompliance). B, Fasting glucose levels improved significantly ($P = .006$). C, HbA_{1c} did not change significantly. BL indicates baseline.

FPLD and GL. Friedman rank analysis was used for nonparametric data. A P value of $<.05$ was accepted as statistically significant.

3. Results

3.1. Baseline characteristics

A total of 6 patients with FPLD were studied (Table 1). The mean age of the patients was 46 years (range, 33-64 years). They had absence of adipose tissue primarily from the extremities with preservation and/or hypertrophy of central adipose tissue. Patients had low to normal total percent body fat (mean, 21.6%; range, 13.7%-27.3%) with relative hypoleptinemia (3.8 ± 0.3 ng/mL) and normal body mass index (BMI) (23.3 ± 0.8 kg/m^2). Two of the 6 patients had a history of pancreatitis. One of these patients also had significant coronary artery disease requiring 4 angioplasties; another patient had evidence of mild cardiac involvement on a dobutamine stress test and is being medically treated.

Five of 6 patients had diabetes (fasting glucose ≥126 mg/dL and/or HbA_{1c} ≥7%), despite attempts to optimize therapy with oral antidiabetic agents and/or insulin (Table 2). All but one patient had hypertriglyceridemia greater than 150 mg/dL (mean, 749 mg/dL; range, 114-2324 mg/dL) despite therapy with fibrates, niacin, or statins. Mean high-density lipoprotein (HDL) was low overall (40 ± 3 mg/dL). Total cholesterol and low-density lipoprotein (LDL) were modestly elevated (mean values of 280 ± 49 and 135 ± 4 mg/dL, respectively). Patients had mild to moderate hepatomegaly (mean, 2138 cm^3; range, 1274-3135 cm^3), consistent with nonalcoholic fatty liver disease. One patient had elevated CRP, whereas the others were in the reference range (Table 2).

3.2. R-metHuLeptin therapy

The patients were enrolled in an open-label study of the effects of r-metHuLeptin on their insulin resistance, diabetes, dyslipidemia, and fatty liver disease. They were observed for 12 months. Serum leptin levels were obtained

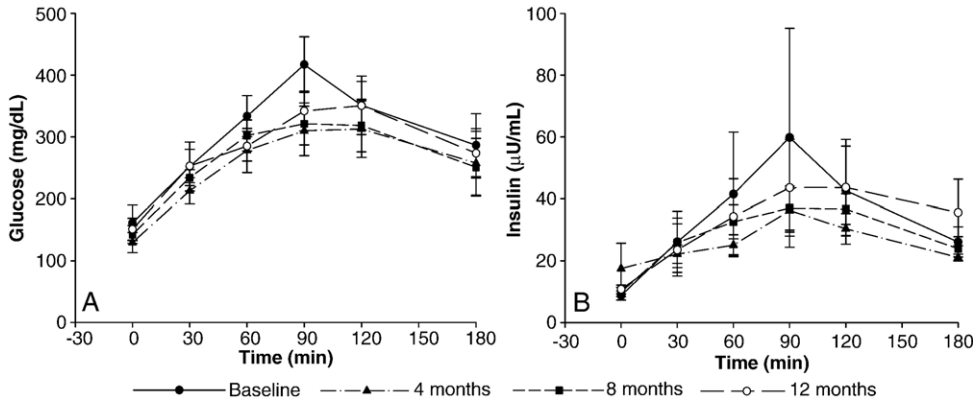

Fig. 2. Oral glucose tolerance test results of 5 patients while on r-metHuLeptin replacement for 12 months. One patient on insulin therapy was not included. A, The difference in glucose levels at each period was not significant. B, The difference in insulin levels during the OGTT at each period was also not significant.

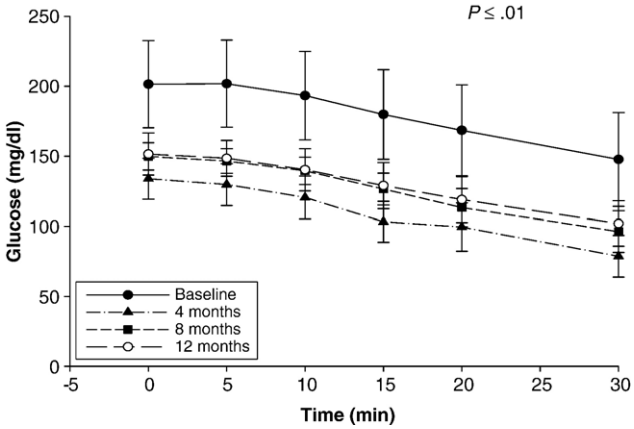

Fig. 3. Insulin tolerance test results of 6 patients while on r-metHuLeptin replacement for 12 months. Glucose levels are followed up after 0.2 U insulin per kilogram of body weight is administered. The difference in serum glucose levels at baseline and subsequent visits were significant ($P < .01$).

after an overnight fast; their last injection of leptin was usually timed 8 to 10 hours prior. R-metHuLeptin was administered to a maximal dose of 0.08 mg/kg per day for each patient. During this period, increased leptin levels were sustained in a range to simulate physiologic levels (Table 3). Several patients were noted to develop nonneutralizing antibodies, which have been found to increase total (free and bound) serum leptin levels.

Subjects reported variable reductions in appetite. There was a moderate reduction in weight (62.1 to 60.2 kg, $P = .03$) and BMI (23.3 to 22.7 kg/m^2, $P < .02$), without significant change in REE (5824 to 5096 kJ per 24 hours, $P = .76$) (Table 3). Other subjective changes, such as changes in energy or heat tolerance, were inconsistent. Furthermore, adrenal (data not shown), thyroid, and growth hormone-related functions were normal at baseline and did not significantly change with r-metHuLeptin therapy (Table 3).

3.3. Effect on lipids

Patients had severe hypertriglyceridemia at baseline. R-metHuLeptin initially led to a 65% reduction in mean triglycerides at 4 months (Table 3). One patient (NIH-21) had elevated triglyceride levels at baseline that were reduced at 4 months, but were variable thereafter because of noncompliance of r-metHuLeptin and lipid-lowering medications (which included niacin and fenofibrate) (Fig. 1A). Analysis of the group with NIH-21 excluded showed a significant decrease in triglyceride levels ($P = .026$).

Total cholesterol decreased (280 to 231 mg/dL, $P = .012$) and LDL levels decreased as well but the change was of borderline significance (135 to 118 mg/dL, $P = .052$). HDL levels were low at baseline and did not change over the course of 12 months (40 to 36 mg/dL, not significant [NS]). Percent body fat (21.6% to 20.2%, NS) and liver volumes (2138 to 1967 mL, NS) had only modest decreases, which were not significant.

3.4. Effect on glycemic control

Five of 6 patients were diabetic before r-metHuLeptin therapy. Leptin led to a significant reduction in fasting glucose (190 to 151 mg/dL, $P = .006$) (Table 3, Fig. 1B). However, the HbA_{1c} (8.4% to 8.0%, NS) remained elevated, representing persistent impairment of glucose tolerance and postprandial hyperglycemia (Table 3, Fig. 1C).

Glucose tolerance test results were markedly abnormal at baseline (Fig. 2A). Despite a reduction in fasting glucose, there was no significant improvement in glucose tolerance after r-metHuLeptin therapy. This was associated with a low insulin response to glucose both at baseline and with r-metHuLeptin therapy (Fig. 2B).

Insulin sensitivity, as reflected by the insulin tolerance test, significantly improved after 4 months and was sustained thereafter (Fig. 3). This likely led to the improvement in fasting glucose levels.

R-metHuLeptin was well tolerated by all patients. For 2 patients (NIH-18 and NIH-21), determining medication compliance was difficult. The discontinuation of r-metHuLeptin for these patients was not a result of side effects. One patient (NIH-21) developed opioid dependence before recombinant leptin therapy while being treated for chronic pancreatitis. She was withdrawn from the study after one and a half years.

Table 4
Antidiabetic therapy of patients during leptin therapy

Parameter	NIH-7		NIH-12		NIH-17		NIH-23	
Time on leptin (mo)	0	54	0	30	0	30	Baseline	24
Triglycerides (mg/dL)	802	164	198	87	550	129	114	229
Fasting glucose (mg/dL)	267	73	181	100	259	123	179	128
HbA_{1c} (%)	9.5	4.5	9.0	7.6	9.7	6.7	8.6	6.1
Oral antidiabetic medications	Pioglitazone	Pioglitazone	Rosiglitazone, glyburide	Rosiglitazone	Glyburide	Rosiglitazone	Pioglitazone, metformin	Pioglitazone, metformin, glimepiride
Daily insulin (U)	110	40	0	50	0	60	0	0

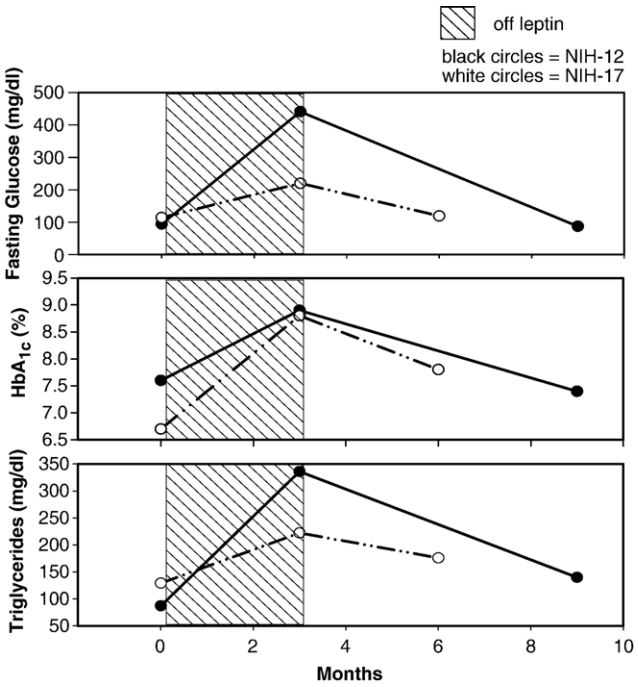

Fig. 4. Clinical course of 2 patients (NIH-12 and NIH-17) after discontinuing r-metHuLeptin replacement for 3 months. During extended follow-up, these 2 patients needed insulin to improve their glycemic control despite treatment with r-metHuLeptin. There is an increase in fasting glucose, HbA_{1c} and triglycerides when r-metHuLeptin was held, which improves after r-metHuLeptin is restarted.

3.5. Extended follow-up

It became apparent that r-metHuLeptin therapy, in addition to oral antidiabetic medications, was not sufficient to normalize glycemia in most patients. This was due in part to their limited insulin responsiveness from long-standing insulin resistance and beta-cell failure. In addition, as noted, the compliance of 2 patients (NIH-18 and NIH-21) was in question, and they were subsequently withdrawn from the protocol.

Table 4 describes the course of the remaining 4 patients. One patient (NIH-23) has done well with the addition of r-metHuLeptin and a sulfonylurea. Another patient (NIH-7) was on insulin before the initiation of r-metHuLeptin, and she has also done well with the addition of r-metHuLeptin; her daily insulin dose was more than halved. The remaining 2 patients (NIH-12 and NIH-17) were started on moderate doses of insulin, which brought their glycemic control to near-target levels.

To confirm whether r-metHuLeptin was effective in these patients, we discontinued r-metHuLeptin in the 2 patients who achieved diabetic control with the addition of insulin. After 3 months of discontinuing r-metHuLeptin, both patients had a dramatic rise in triglyceride, fasting glucose, and HbA_{1c} levels (Fig. 4). R-metHuLeptin was then resumed in these patients. Both patients improved within 3 to 6 months, whereas insulin and oral antidiabetic and lipid-lowering agents were kept at the same doses.

3.6. Comparison of patients with FPLD and patients with GL

It is important to note the baseline differences between patients with FPLD and those with GL (Fig. 5). In a previous article, we reported the long-term effects of leptin replacement in patients with GL [11]. In comparison to the

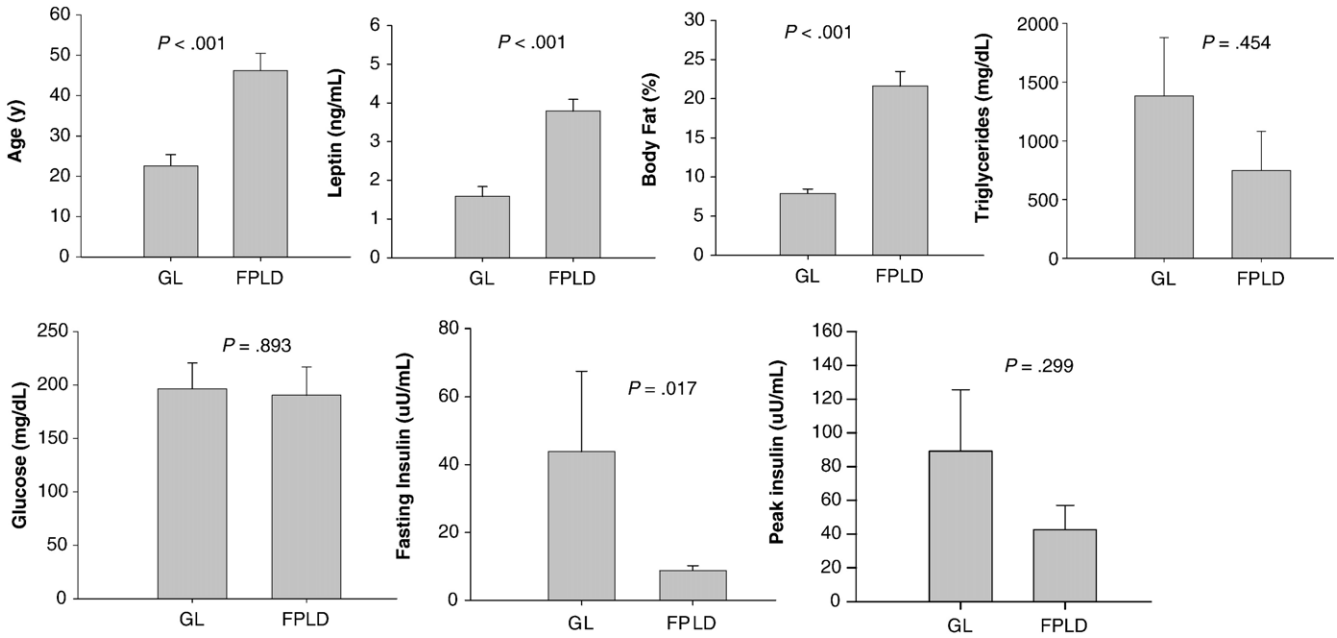

Fig. 5. A comparison of patients with GL and FPLD at baseline. Patients with FPLD are older and have higher leptin levels and body fat. Baseline fasting glucose and triglyceride levels are similar. Patients with FPLD have fasting insulin levels that are significantly lower for similar fasting glucose levels. Peak insulin levels during OGTT were not significantly different.

patients with GL, patients with FPLD were older and had higher percent body fat and leptin levels. Patients with FPLD also had lower insulin levels for the same degree of hyperglycemia, both in the basal state and 2 hours after oral glucose. During extended follow-up, 9 of the 15 patients with GL reported to be on insulin at baseline are now only 2 of 15 patients ([11], Phillip Gorden, unpublished observation, March 2006). In contrast, 1 of the 4 patients with FPLD was on insulin at baseline and 3 of the 4 patients were on insulin during extended follow-up. Mean triglyceride levels were not significantly different between patients with FPLD and GL (Fig. 5). Median levels were similar; the patients with FPLD and GL had triglyceride levels of 527 and 523 mg/dL, respectively. Because triglyceride levels were not a normal (Gaussian) distribution, they are difficult to compare. Peak levels for patients with FPLD were 2000 mg/dL, although several patients with GL had values higher than this, with peak levels at 7420 mg/dL [11].

4. Conclusions

This is the first study to examine the effect of replacement r-metHuLeptin therapy over an extended period in patients with FPLD. These patients demonstrate an improvement in insulin sensitivity, fasting glucose concentrations, and triglyceride levels. These changes are similar to those seen in GL but less dramatic. Patients with FPLD have a number of differences at baseline from patients with GL. Patients with FPLD and GL are similar in that both are insulin resistant and have diabetes and dyslipidemia, but these abnormalities are more severe in GL. There are other differences of significance: The patients with FPLD are older, have had diabetes for a longer time, and have higher serum leptin concentrations. Patients with GL have a more dramatic response to leptin therapy than patients with FPLD. This could be related to the lower circulating leptin levels in the patients with GL, but it is also clear that the patients with FPLD have lower baseline and stimulated insulin responses. Thus, the patients with FPLD, like patients with type 2 diabetes mellitus, may require exogenous insulin administration to achieve American Diabetes Association–recommended therapeutic targets for HbA_{1c}. We have interpreted the improvement in fasting glucose to be related to improvement in insulin sensitivity as shown by insulin tolerance tests, previously validated by the euglycemic clamp [21]. We also suggest that the impoverished endogenous insulin secretion in response to glucose is the major reason for the lack of significant improvement in glucose tolerance in these 6 subjects.

Throughout the 12 or more months of our study, r-metHuLeptin was tolerated well with no reported side effects. In our previous report of r-metHuLeptin therapy for patients with GL, there were similar findings. Fifteen patients tolerated the treatment well; 5 patients were withdrawn from the study for reasons not related to any side effects [11].

The number of patients with FPLD in this study is small, but the variability of the metabolic disorders is typical of the heterogeneity seen in these patients [22,23]. This is well represented by the triglyceride levels, where pretreatment levels ranged from normal to more than 2000 mg/dL. Because of the magnitude of this abnormality, we see a significant response to leptin treatment, an effect that is not seen with other modalities of treatment [24]. Thus, all of our patients with elevated triglyceride levels were treated with maximal doses of thiazolidinediones and lipid-lowering agents (statins or fibrates) before leptin administration. Although leptin administration significantly improves fasting glucose levels, it does not significantly change glucose values as measured by HbA_{1c} or glucose tolerance over the long term. We suggest that this is due to the depressed endogenous insulin response in patients with FPLD compared with patients with GL. Furthermore, leptin administration to patients with type 1 diabetes mellitus with lipodystrophy and insulin resistance will improve insulin sensitivity, but insulin is still required (Phillip Gorden, unpublished observation, September 2001). Thus, low-dose leptin replacement cannot substitute for severe insulin deficiency in FPLD or type 1 diabetes mellitus.

Leptin administration to obese patients essentially defined the concept of clinical leptin resistance, where high doses of leptin had only a modest effect on body weight [5]. More recent studies, however, suggest that leptin administration to obese patients who have lost only 10% of their body weight does affect more subtle parameters, such as the degree in fall of energy expenditure or reduction in thyroid hormone values [25].

The lipodystrophy model offers the opportunity to define the threshold of leptin response to metabolic parameters, but this study makes it clear that this is not straightforward. Other factors such as insulin secretion complicate this interpretation. The highest doses of leptin used in these patients were administered to simulate high physiologic ranges. Whether the higher doses of leptin previously used in obese patients would be effective in patients with FPLD has not been determined.

Other forms of treatment are available for patients with FPLD and HIV lipodystrophy. Thiazolidinediones have been used with limited success in both groups of patients who possess variable amounts of normal adipose tissue [24,26-28]. Because thiazolidinediones have been shown to induce peroxisome proliferator–activated receptor γ in the liver of lipodystrophic rodents, we do not use these medications in our patients with GL [29]. Ultimately, patients with FPLD often needed to be on multiple medications including insulin for glucose control and lipid-lowering agents for dyslipidemia. Although conventional treatment (ie, oral antidiabetic medications and insulin) may be adequate for glucose control, dyslipidemia, pancreatitis, and NASH remain as major therapeutic problems. For these problems, leptin therapy has a special role, because conventional treatment alone often did not improve these parameters optimally.

For the patients with FPLD and GL in our study, our data suggest that leptin increases insulin sensitivity, has an inhibitory effect on lipogenesis, and stimulates fatty acid oxidation throughout the body. This is primarily manifested by reduced circulating triglycerides and hepatic steatosis. This is consistent with rodent data where lipodystrophic mice were treated with leptin. Stearoyl-CoA desaturase-1, an enzyme involved in lipogenesis, had decreased activity in the liver, reducing hepatic steatosis [30]. Leptin has also been shown to increase fatty acid oxidation in mice by activating 5′ -adenosine monophosphate–activated protein kinase and inhibiting the activity of acetyl coenzyme A carboxylase [31]. The reduction in lipids in both human muscle and liver is associated with increased insulin sensitivity. Whether this is a central or peripheral mechanism of leptin cannot be determined. It seems clear that the effects are not occurring by reduction of food intake alone [10,11].

In conclusion, a preliminary picture is emerging where recombinant leptin may have a special therapeutic role. There are metabolic abnormalities such as NASH that improve with leptin treatment in lipodystrophy patients [11,12]. Hypothalamic amenorrhea in hypoleptinemic lipodystrophic patients as well as normal hyperexercised or low-weight amenorrheic patients also respond to leptin treatment [32-34]. Patients with insulin receptor mutations and extreme insulin resistance also had partial, but significant improvement, in fasting glucose, HbA_{1c}, glucose, and insulin tolerance [35]. Clearly, leptin has a special role in the treatment of congenital leptin deficiency and generalized forms of lipodystrophy. We now show for the first time that partial forms of lipodystrophy with relatively low leptin levels (but higher than those seen in GL) respond to r-metHuLeptin administration over at least 12 months.

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