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ARTICLE

Efficacy of leptin therapy in the different forms of human lipodystrophy

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Abstract
Aims/hypothesis Lipodystrophy is a rare disorder characterised by loss of adipose tissue, hypoleptinaemia, severe insulin resistance, diabetes and dyslipidaemia. The aims of this study were to determine whether leptin replacement in lipodystrophy patients ameliorates their metabolic abnormalities over an extended period of time and whether leptin therapy is effective in the different forms of lipodystrophy.
Methods We conducted an open-label prospective study of patients with acquired forms of lipodystrophy and inherited forms of lipodystrophy secondary to mutations in the *AGPAT2*, *SEIPIN* (also known as *BSCL2*), *LMNA* and *PPARγ* (also known as *PPARG*) genes. Between July 2000 and November 2008, 48 patients with lipodystrophy were treated with s.c. recombinant methionyl human leptin.
Results Serum triacylglycerol and HbA_{1c} levels declined dramatically with leptin therapy. Among 35 patients with data at baseline and 12 months, serum triacylglycerol fell by 59% (from 10.18±2.67 mmol/l to 4.16±0.99 mmol/l [means±SE]; $p=0.008$) and HbA_{1c} decreased by 1.5 percentage points (from 8.4±0.3% to 6.9±0.3%; $p<0.001$). A significant reduction was seen in total cholesterol and a trend towards reduction was observed in LDL-cholesterol at 12 months. HDL-cholesterol was unchanged. Among generalised lipodystrophy patients, proteinuria diminished with leptin replacement. Patients with both acquired and inherited forms of lipodystrophy experienced decreases in serum triacylglycerol and HbA_{1c} levels.
Conclusions/interpretation Leptin replacement in lipodystrophy patients leads to significant and sustained improvements in glycaemic control and dyslipidaemia. Leptin is effective in the various forms of lipodystrophy, whether they are acquired or inherited, generalised or partial.

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Keywords Diabetes · Insulin resistance · Leptin · Lipodystrophy

Abbreviation

AGPAT patients	Patients with mutations in the *AGPAT2* gene
LMNA patients	Patients with mutations at position 482 in the *LMNA* gene
PPARγ patients	Patients with mutations in the *PPARγ* gene
r-metHuLeptin	Recombinant methionyl human leptin
SEIPIN patients	Patients with mutations in the *SEIPIN* gene

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Introduction

Lipodystrophy, the selective loss of adipose tissue, is a phenotypic feature of a number of different conditions. Both inherited and acquired forms exist and involvement can be generalised or partial. In recent years, considerable

progress has been made in distinguishing various genetic types of lipodystrophy. Regardless of the type of lipodystrophy, all forms share a common metabolic set of abnormalities that include hypertriacylglycerolaemia, other dyslipidaemias, insulin resistance and diabetes. The aetiology of this cluster of abnormalities appears to be relative hypoleptinaemia.

Initial studies in rodent models suggested that leptin replacement by injection, fat transplantation or genetic manipulation would correct the constellation of metabolic derangements associated with lipodystrophy [1–3]. We have presented early evidence to show that this effect of leptin is also true in patients with lipodystrophy [4]. Further studies by our group and others have confirmed this finding [5–10].

In the present study, we now demonstrate (1) that leptin therapy is effective in improving metabolic abnormalities over an extended period of time, and (2) most importantly, that it is effective in all the various forms of lipodystrophy.

Methods

Patient population Between July 2000 and November 2008, we treated a total of 48 patients who had either generalised or partial lipodystrophy (acquired or inherited). The patients were from the USA and a number of other countries in Europe and South America. Inclusion criteria for recombinant methionyl human leptin (r-metHuLeptin) therapy were relative hypoleptinaemia (highest baseline serum leptin was 12.2 μg/l); metabolic abnormalities, such as fasting hypertriacylglycerolaemia (>2.26 mmol/l), diabetes mellitus or fasting hyperinsulinaemia (>208 pmol/l); and the ability to adhere to leptin therapy and the protocol regimen. Our study population did not include patients with lipodystrophy related to infection with the human immunodeficiency virus.

Patients were classified according to lipodystrophy type. 'SEIPIN' patients had mutations in the *SEIPIN* (also known as *BSCL2*) gene, 'AGPAT' patients had mutations in the *AGPAT2* gene and 'PPARγ' patients had mutations in the *PPARγ* (also known as *PPARG*) gene. In this paper, the 'LMNA' classification refers to patients with Dunnigan-type familial partial lipodystrophy who had mutations at position 482 in the *LMNA* gene. The genetic analyses were primarily performed in the laboratory of A. Garg (University of Texas Southwestern Medical Center, Dallas, TX, USA); some were also carried out in the laboratories of J. Magré (INSERM, Paris, France) and R. Hegele (University of Western Ontario, London, ON, Canada). The term 'acquired' was used for patients who clearly did not have an inherited form of lipodystrophy by clinical history. Four of the 48 patients had an inherited form of lipodystrophy by family history, but did not carry one of the mutations known to cause lipodystrophy. These patients were classified as 'unknown'.

r-metHuLeptin for the trial was provided by Amgen (Thousand Oaks, CA, USA) from 2000 to 2007 and by Amylin Pharmaceuticals (San Diego, CA, USA) from 2007 onwards. Although Amgen and then later Amylin provided the recombinant leptin, the data were held and analysed by the academic investigators. r-metHuLeptin therapy was given as a self-administered once- or twice-daily s.c. injection as previously described [4, 8, 10]. In the earlier years of the protocol, the dose was escalated to the full dose over the first 2 months of treatment. In later years, we increased the dose over a few weeks. After dose escalation, the usual replacement dose was 0.08–0.12 mg $kg^{-1} day^{-1}$ in an attempt to simulate the normal to high physiological range. More recently, the dose has been increased to 0.24 mg $kg^{-1} day^{-1}$ in a few patients.

At baseline, patients were on conventional medications for diabetes and dyslipidaemia. These medications were subsequently decreased or discontinued as clinically indicated. Patients were evaluated at the Clinical Research Center of the National Institutes of Health. Data were collected during inpatient admissions to a metabolic unit.

The protocol was approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases. Informed consent was obtained from each patient or his/her legal guardian.

Biochemical analyses Levels of serum leptin, HbA_{1c}, glucose and lipids were measured as previously described [4, 8, 10, 11]. All serum values represent morning fasting levels and samples were collected on the first full day of the inpatient stay. Urinary protein was determined as previously described [12].

Procedures After an overnight fast, patients underwent an OGTT in which 1.75 g/kg to a maximum of 75 g of oral glucose was administered.

Per cent body fat was determined using whole body dual-energy x-ray absorptiometry (QDR 4500; Hologic, Bedford, MA, USA). The body fat percentage was reported for the subtotal region, which excludes the head.

Statistical analyses Values are expressed as means±SE. Paired two-tailed *t* tests were used whenever applicable to compare baseline data with data obtained at various times. SAS software (Cary, NC, USA) was used to calculate AUCs for serum glucose vs time in OGTTs. $p<0.05$ was accepted as statistically significant.

Results

Baseline characteristics of treated patients The baseline demographic characteristics of all our patients treated with

Table 1 Baseline demographic characteristics of study participants according to lipodystrophy type

Lipodystrophy type	*n*	Per cent female	Median age at baseline, years (range)	Previously reported cases (NIH case number and reference)
Acquired	12	67	17.5 (10–68)	NIH-1 [4, 8, 11, 12, 26, 27, 29], NIH-3 [4, 8, 11, 12, 29], NIH-9 [4, 8, 9, 11, 12, 26], NIH-10 [12], NIH-14 [11, 12, 27], NIH-15 [11, 12, 27], NIH-19 [8, 12, 27], NIH-28 [9]
AGPAT	13	92	17 (13–47)	NIH-2 [4, 8, 11, 12, 26, 29], NIH-4 [4, 8, 11, 12, 26, 29], NIH-5 [4, 8, 11, 12, 26, 29], NIH-6 [4, 8, 11, 12, 26, 27, 29], NIH-8 [4, 8, 11, 12, 26, 27], NIH-11 [8, 11, 12, 26], NIH-16 [8, 27], NIH-20 [8, 12, 27], NIH-22 [8, 12]
SEIPIN	7	57	13 (8–17)	NIH-13 [8, 11, 12], NIH-24 [8, 12]
LMNA	9	100	42 (18–65)	NIH-7 [4, 10, 11, 26, 27, 29], NIH-12 [10, 11, 26, 27], NIH-17 [10], NIH-18 [10], NIH-21 [10], NIH-23 [10]
PPARγ	2	100	33.5 (32–35)	NIH-29 [7]
Unknown	4	100	22.5 (11–35)	

This table does not include one patient (male, aged 8 years) who had atypical Werner syndrome secondary to a mutation in the *LMNA* gene. He had only baseline data

NIH, National Institutes of Health

leptin between July 2000 and November 2008 are given in Table 1. We administered leptin to 48 patients, 39 of whom were female (81%). The median baseline age was 18 years with a range of 8–68 years. The mean baseline serum leptin level was 2.53±0.40 μg/l and the mean baseline body fat was 11.7±1.0%.

Response to leptin therapy Forty-eight patients were treated with leptin for varying periods of time. Forty-three out of 48 were followed on leptin for at least 4 months. Some patients have been treated for >8 years. Initially, all patients were treated with a standard leptin dose according to protocol [4]. Over time, the maximum dose of leptin administered to an individual patient was increased based on the severity of metabolic derangements. The leptin doses used ranged from 0.04 to 0.24 mg $kg^{-1}day^{-1}$, with the majority of patients receiving between 0.08 and 0.12 mg $kg^{-1}day^{-1}$ (Fig. 1).

The serum triacylglycerol levels for all treated patients over time are depicted as box plots in Fig. 2a. Serum triacylglycerol ranged widely at baseline and progressively decreased over time with leptin replacement. The mean serum triacylglycerol for all treated patients over time is shown in Fig. 2b. The mean triacylglycerol level of patients at 12 months of follow-up was 51% lower than the mean level of patients at baseline. The mean at 18 months and beyond was 66% lower than the mean of patients at baseline.

Box plots of HbA_{1c} levels for all treated patients over time are provided in Fig. 3a. Figure 3b depicts the mean HbA_{1c} of all treated patients over time. The mean HbA_{1c} fell below the target of 7% over the course of leptin therapy.

Thirty-five patients had serum triacylglycerol and HbA_{1c} values at baseline and 12 months (Table 2). Among these 35 patients, serum triacylglycerol dropped significantly, from 10.18±2.67 mmol/l at baseline to 4.16±0.99 mmol/l at 12 months (p=0.008). HbA_{1c} was significantly reduced from 8.4±0.3% at baseline to 6.9±0.3% at 12 months (p<0.001). There was also a significant decrease in total cholesterol and a trend towards a decrease in LDL-cholesterol (Table 2), but, as previously described [8, 10], no significant change in HDL-cholesterol was observed.

Thirty-two patients had OGTT data at baseline and after 12 months of leptin therapy (Fig. 4). Leptin treatment led to a significant decrease in fasting serum glucose in the OGTT from baseline to 12 months (9.10±0.70 vs 7.15±0.64 mmol/l, p=0.014). The AUC of serum glucose vs time during the OGTT (Fig. 4) was also significantly reduced from baseline (2,696±157 vs 2,199±173 mmol/l× min, p=0.006). The improvement in glucose tolerance occurred even though most patients had a reduction in their glucose-lowering medications (Table 3).

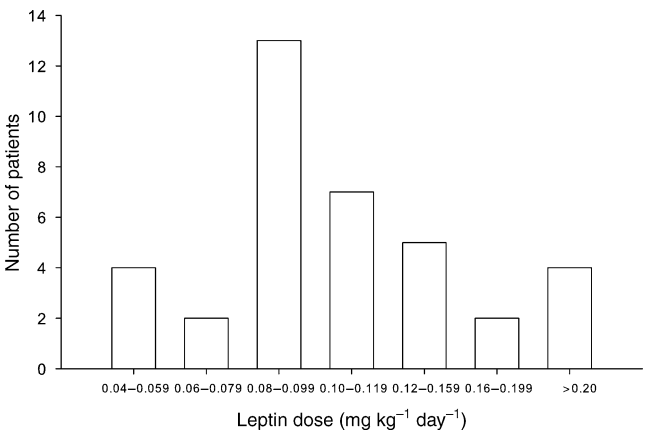

Fig. 1 Leptin doses in November 2008 for patients actively being treated on protocol. For each individual patient, the leptin dose varied over time. In general, however, the majority of patients were on 0.08–0.12 mg $kg^{-1}day^{-1}$

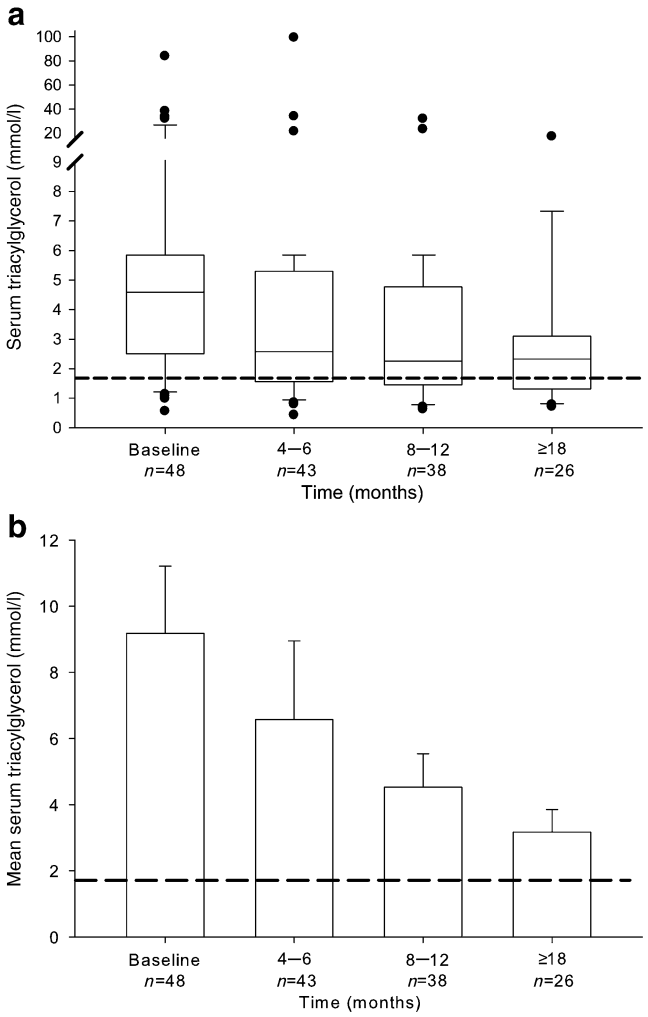

Fig. 2 Serum triacylglycerol of all leptin-treated patients over time. The dashed line represents target value of 1.69 mmol/l. **a** Box plots with the line in the middle of the box representing the median value, the bottom of the box representing the 25th percentile, and the top of the box representing the 75th percentile. The upper whisker corresponds to the 95th percentile and the lower whisker corresponds to the 5th percentile. Dots represent outliers. **b** Mean levels+SE

Effect of leptin on urinary protein We have previously reported that generalised lipodystrophy can be associated with clinical and nephrotic-range proteinuria and that this proteinuria can be ameliorated with leptin therapy [12, 13]. The decrease in proteinuria with leptin replacement is accompanied by a reduction in creatinine clearance and hyperfiltration [12, 13]. In six patients, the nature of the renal dysfunction was determined by renal biopsy [13]; however, the specific aetiology of proteinuria was not known for the majority of patients. In patients with generalised lipodystrophy, urinary protein excretion tended to decline over time with leptin replacement. The mean 24 h urinary protein excretion of generalised lipodystrophy patients evaluated at 12 months was 51% lower than the mean of patients at baseline (1.843 vs 0.901 g, Fig. 5). Of note, the data at baseline and 12 months include two patients with membranoproliferative glomerulonephritis who had marked exacerbations in proteinuria while on leptin replacement [12].

While many of our patients are on ACE inhibitors because of proteinuria, we have noticed elevated blood pressure in only a few patients and no consistent changes during leptin therapy.

Baseline characteristics of different types of lipodystrophy Patients were analysed by lipodystrophy type. The mean baseline serum leptin level for acquired patients was 1.31±0.28 μg/l, for AGPAT 1.81±0.50 μg/l, for SEIPIN 0.68±0.13 μg/l, for LMNA 4.62±0.79 μg/l and for PPARγ 5.87±2.14 μg/l (Fig. 6a). The mean baseline body fat for acquired patients was 7.7±0.6%, for AGPAT 8.5±0.9%, for SEIPIN 8.8±0.4%, for LMNA 20.8±1.4% and for PPARγ 19.1±4.3% (Fig. 6b). Patients with generalised forms of lipodystrophy (acquired, AGPAT and SEIPIN) tended to have

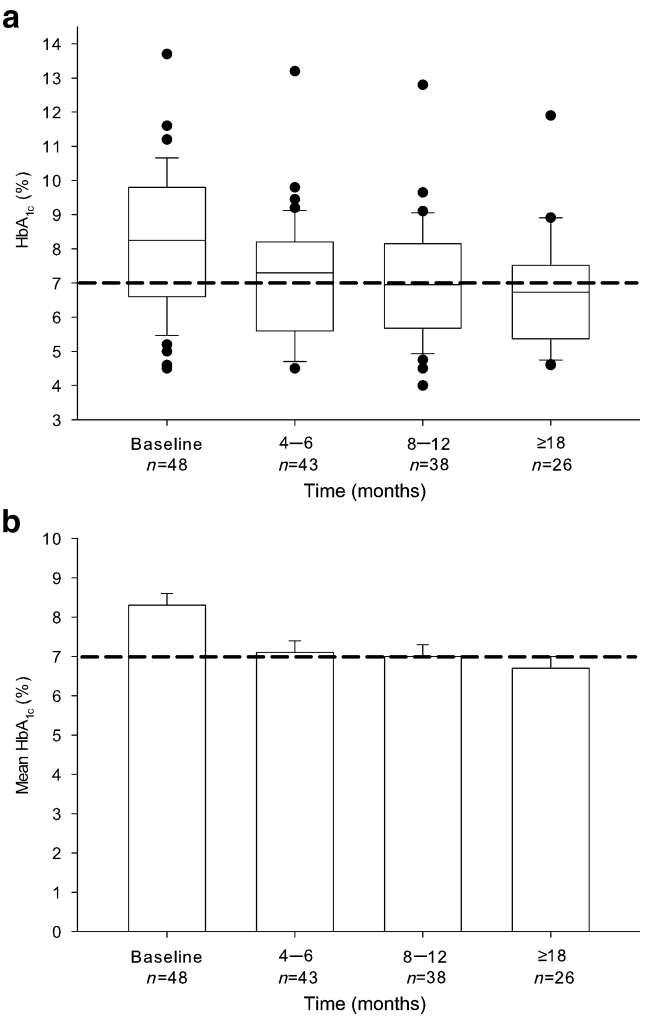

Fig. 3 HbA_{1c} of all leptin-treated patients over time. Dashed line represents target value of 7.0%. **a** Box plots. **b** Mean levels+SE

Table 2 Biochemical changes in leptin-treated patients who had data at baseline and 12 months

Variable	Baseline	12 months	*n*	*p* value[a]
HbA_{1c} (%)	8.4±2.0	6.9±1.7	35	<0.001
Triacylglycerol (mmol/l)	10.18±2.67	4.16±0.99	35	0.008
Total cholesterol (mmol/l)	6.03±0.52	4.25±0.20	35	<0.001
LDL-cholesterol (mmol/l)	2.85±0.30	2.32±0.13	26[b]	0.082
HDL-cholesterol (mmol/l)	0.83±0.05	0.80±0.04	35	0.312

[a] Paired two-tailed *t* test

[b] In some patients, LDL-cholesterol could not be determined because serum triacylglycerol was >4.52 mmol/l

lower baseline leptin levels and per cent body fat than those with partial forms of lipodystrophy (LMNA and PPARγ).

Response of different types of lipodystrophy to leptin therapy The 35 patients who had serum triacylglycerol and HbA_{1c} values at baseline and at 12 months were grouped according to lipodystrophy type. The values for each patient are plotted in Fig. 7. In the acquired lipodystrophy group, the range of baseline serum triacylglycerol was very wide. All of seven patients with acquired lipodystrophy had a dramatic reduction in serum triacylglycerol over 12 months. AGPAT2 patients also had a large range of serum triacylglycerol at baseline. Eleven of 12 AGPAT patients experienced a marked drop in triacylglycerol after 12 months of leptin replacement. Interestingly, compared with acquired and AGPAT patients, SEIPIN patients had much lower levels of and less variation in their serum triacylglycerol at baseline. Four of six SEIPIN patients had a modest decrease in their triacylglycerol over 12 months. All LMNA patients experienced a reduction in serum triacylglycerol after 12 months of leptin therapy. There were only two PPARγ patients; one had a 53% decrease in serum triacylglycerol and the other had a 32% increase.

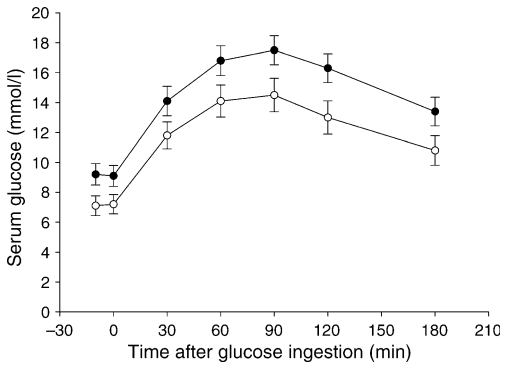

Fig. 4 OGTT data at baseline and 12 months in 32 leptin-treated patients. Black circles, baseline; white circles, 12 months. Error bars represent SE. Fasting serum glucose and AUCs were significantly lower at 12 months than at baseline

All of seven acquired lipodystrophy patients experienced a reduction in HbA_{1c} from baseline to 12 months. Eleven of 12 AGPAT patients also had a drop in HbA_{1c} after 12 months of leptin treatment. In contrast to serum triacylglycerol, HbA_{1c} values in SEIPIN patients at baseline had a distribution that was similar to that of acquired and AGPAT patients. Four of six SEIPIN patients had a drop in HbA_{1c} after 12 months of therapy. Five of six LMNA patients and both of two PPARγ patients showed a decrease in HbA_{1c} over 12 months.

Non-adherence vs resistance to leptin therapy The data reported in this paper were collected on the morning of the first full day of an inpatient admission and largely reflect the outpatient status of the patients. In some patients, we noticed an initial response to leptin therapy followed by an apparent relapse in metabolic abnormalities. Two examples are shown in Fig. 8. In patient NIH-1, the issue was dietary non-adherence. With modest control of her diet, her triacylglycerol levels became well controlled over the course of an inpatient stay. In patient NIH-37, her problems with metabolic control probably stemmed from non-adherence both to diet and to leptin and insulin treatment.

We have not documented a case of refractoriness to leptin replacement. Thus far, relapses in metabolic derangements appear to be related to medical non-adherence. Over

Table 3 Insulin and oral glucose-lowering medication use in 32 leptin-treated patients with OGTT data at baseline and 12 months

No. of patients	Baseline	12 months
On insulin	13 of 32 (120–5,000 U/day)	7 of 32 (40–1,200 U/day)[a]
On oral agents	23 of 32	19 of 32

[a] The dose of 1,200 U/day represents the requirements of one patient (NIH-32), who has acquired lipodystrophy and juvenile dermatomyositis. If NIH-32 is excluded, the highest daily dose of insulin being used as of November 2008 was 160 U

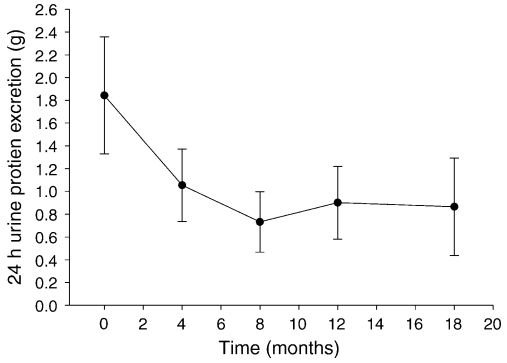

Fig. 5 Twenty-four hour urinary protein excretion of patients with generalised lipodystrophy at baseline and while on leptin therapy. n= 29, 28, 21, 21 and 18 at 0, 4, 8, 12 and 18 months, respectively. Error bars represent SE. For further detail, see Javor et al. [12]

the course of more than 8 years, leptin therapy has been discontinued in eight patients after 3–29 months because of non-compliance. It has been restarted in four of these patients at their request.

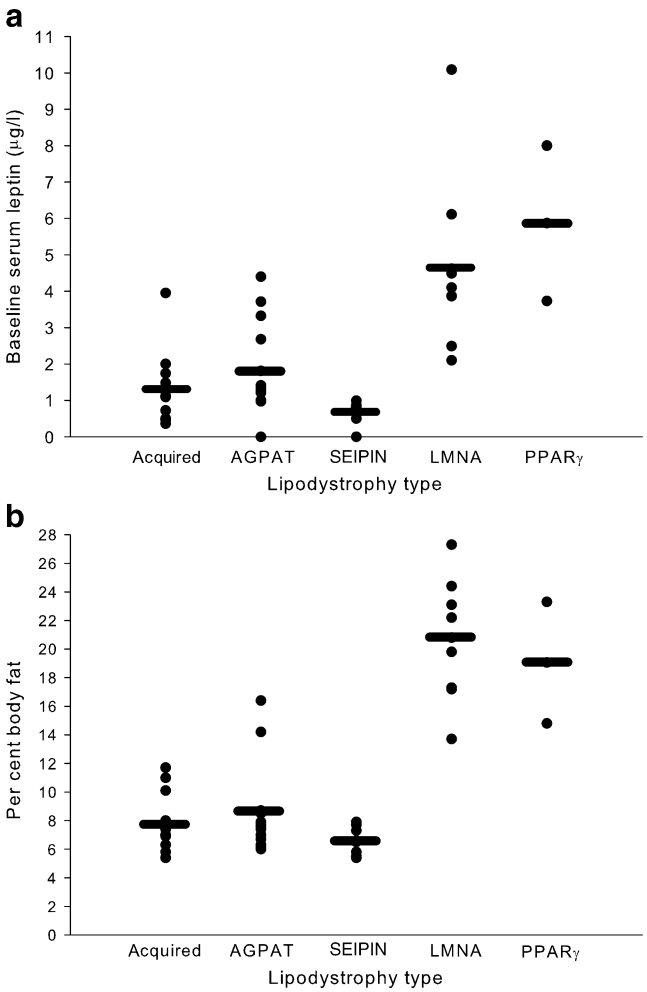

Fig. 6 Baseline serum leptin (**a**) and per cent body fat (**b**) grouped according to lipodystrophy type. Each dot represents an individual patient. The mean in each group is represented by a horizontal black line

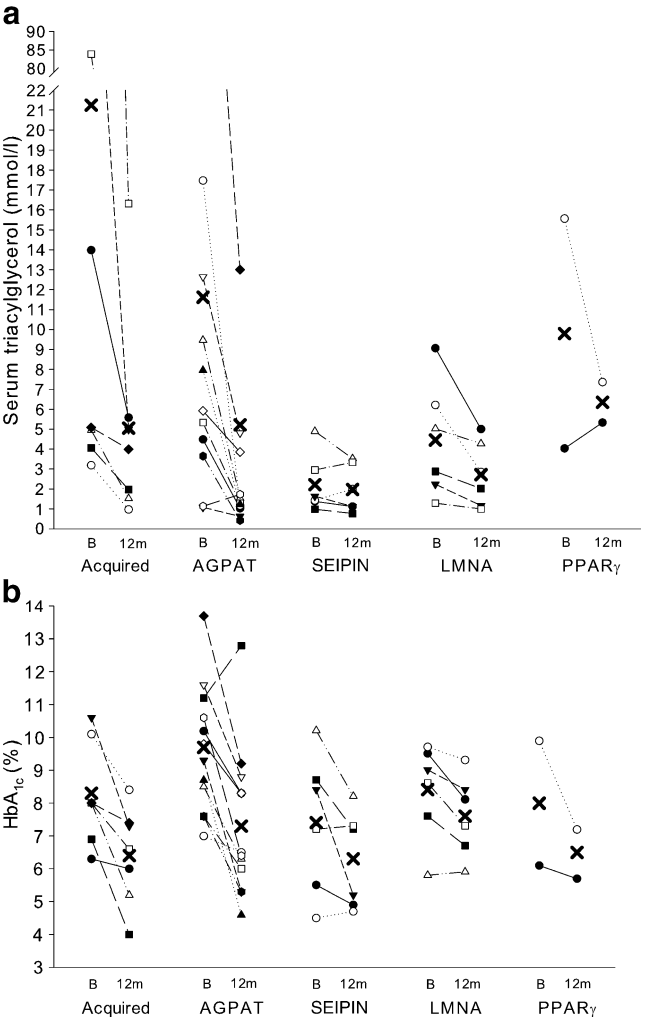

Fig. 7 Serum triacylglycerol (**a**) and HbA_{1c} (**b**) of 35 leptin-treated patients at baseline (B) and 12 months (12 m) of leptin therapy. Crosses represent mean values

Comorbid conditions The various forms of lipodystrophy represent serious medical conditions [8, 12, 13]. For instance, two patients whom we evaluated for leptin replacement died of cardiac and pulmonary causes and never received treatment. These two patients were not included in the 48 patients analysed in this paper. Two other patients died of cardiac and renal causes after leptin had been discontinued for 1–2 years. We have previously discussed the exacerbation of renal disease in two patients while on leptin [12]. Three patients on leptin therapy have undergone kidney transplantation. Two of these three were treated with leptin before the onset of renal failure, during dialysis and after renal transplantation. One patient was started on leptin only after transplantation. Two patients with acquired lipodystrophy who had immunodeficiency documented prior to leptin initiation developed T cell lymphoma after 8 months of leptin therapy. The association of acquired lipodystrophy with T cell lymphoma has been reported in the absence of

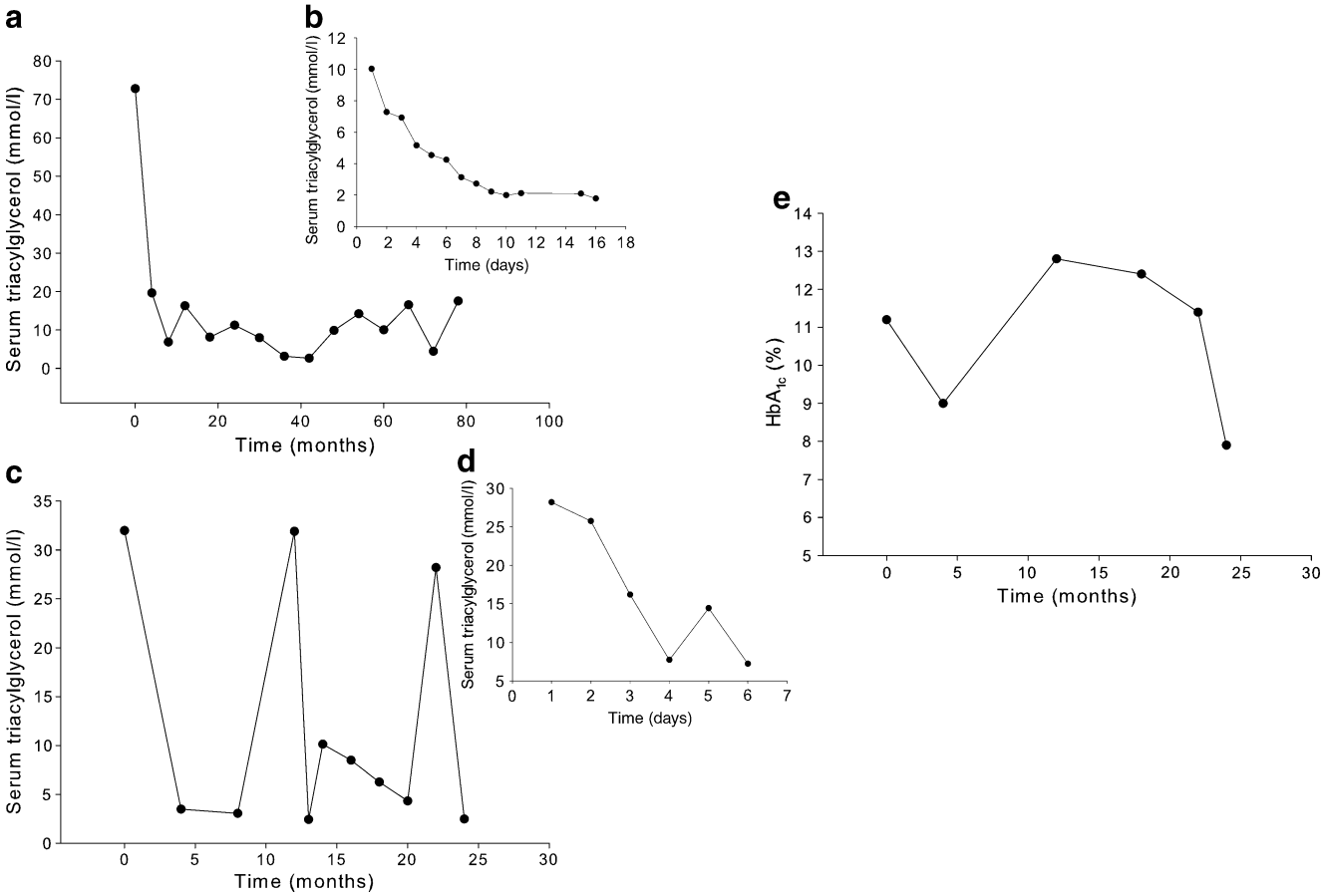

Fig. 8 **a** Serum triacylglycerol of patient NIH-1 on leptin therapy. **b** Serum triacylglycerol of patient NIH-1 on leptin therapy while on a controlled high monounsaturated fat diet at a 60 month follow-up admission. Note that, over time, serum triacylglycerol fluctuates between 2.64 and 19.64 mmol/l on follow-up visits. **c** Serum triacylglycerol of patient NIH-37 on leptin therapy. **d** Serum triacylglycerol of patient NIH-37 on leptin therapy while on a controlled high monounsaturated fat diet at a 22 month follow-up admission. Under observation at the Clinical Research Center, the serum triacylglycerol decreased by 74% over 6 days. At 22 months, the leptin dose was increased from 0.10 to 0.20 mg $kg^{-1}day^{-1}$. **e** HbA_{1c} of patient NIH-37 on leptin therapy. At the 24 month follow-up visit, HbA_{1c} was 7.9% and insulin was no longer required

leptin treatment [14]. While we cannot determine whether leptin therapy played a role in the development of T cell lymphoma, we are concerned about administering leptin to patients with acquired lipodystrophy who have evidence of bone marrow suppression and lymphadenopathy.

Pancreatitis has also been a frequent comorbid feature of all forms of lipodystrophy, presumably because of the severe hypertriacylglycerolaemia. One patient died of haemorrhagic pancreatitis after discontinuing leptin against medical advice. We have found that following leptin therapy, symptoms and laboratory features of pancreatitis have been extremely uncommon.

Discussion

In this study, we present the largest assembly of data to date on leptin therapy in lipodystrophy. The patients on this report comprise multiple different ethnicities and reside in the USA and 12 other countries. We confirm that leptin administration is effective in ameliorating the major metabolic abnormalities seen in lipodystrophy. Furthermore, leptin replacement continues to be effective over a prolonged period of time. Most importantly, we present data to indicate that all the subtypes of lipodystrophy respond to leptin therapy. It must be acknowledged, however, that our study is small and not a randomised, controlled trial. The limitations of our study must be considered in evaluating the data presented. Because of our protocol design, we observed the initial effects of leptin therapy at 4 months. However, when patients are followed more closely, the effects can be observed within days [6].

There was selection bias in our study population since we deliberately chose hypoleptinaemic individuals to demonstrate proof of principle that leptin replacement is effective. Currently, we know that leptin resistance is seen in obese

patients with hyperleptinaemia [15]. We do not know what the limiting endogenous leptin level is for exogenous leptin therapy to have an effect. Although we have preliminary information that increasing the exogenous leptin dose may be effective, the maximum dose we have administered is still less than that used in the initial obesity studies [15].

In some patients, we noted an initial response to leptin replacement with subsequent apparent refractoriness. When we investigated more carefully, we found that this seeming lack of response to leptin was caused by non-compliance with the treatment regimen rather than refractoriness to leptin itself. Patients may not adhere to leptin therapy, glucose-lowering medications or diet. Many patients have severe dyslipidaemia and insulin resistance, and some continue to require some form of adjunctive therapy (e.g. insulin and conventional lipid-lowering drugs) for maximal benefit. While our observations about potential refractoriness and dosing schedules are preliminary in nature, they are important considerations in the practical care of these patients.

Lipodystrophy is a complex condition with many different aetiologies, but the primary metabolic derangement in this condition appears to be caused by leptin deficiency. While we now know that many adipokines exist, leptin is the only one to be administered to patients. Therefore, leptin is the only adipokine we know that has direct biological relevance in humans. Clinically, one of the earliest and most dramatic effects of leptin in lipodystrophy patients is to decrease the marked hyperphagia [4, 6, 11, 16]. The decrease in energy intake is associated with mild initial weight loss and a decrease in resting energy expenditure [4, 8, 11]. There is also a decrease in insulin resistance in liver and muscle [17, 18]. This improved insulin sensitivity is associated with removal of ectopic fat from these two types of tissue [17, 18].

There are a number of molecules activated in leptin-treated rodents that could affect lipid and glucose metabolism. For example, the leptin-mediated activation of AMP kinase may be involved in stimulating lipid oxidation [19–22]. The repression of stearoyl-CoA desaturase-1 by leptin may contribute to decreased lipid synthesis [23, 24]. The effect of leptin on the activity of AMP kinase and stearoyl-CoA desaturase-1 may be involved in increasing insulin sensitivity. AMP kinase and stearoyl-CoA desaturase-1 are just two of several molecules thought to be important in the leptin-signalling pathway [19–22, 25]. Whether the actions of leptin are predominantly central, peripheral or both in patients cannot be determined from our study.

In addition to metabolic abnormalities, lipodystrophy may be associated with cardiac, renal, hepatic and immunological dysfunction. We have previously discussed the issue of renal disease in patients with generalised lipodystrophy [12, 13]. Proteinuria is very common in these patients and may have a complex aetiological basis. Regardless of the aetiological complexity, leptin therapy is associated with a decrease in urinary protein excretion.

Under the conditions of this research protocol, there is a mild effect of leptin on circulating T cells and cytokine production [26]. When treating a rare disease that has many comorbid conditions, it is difficult to know whether a therapeutic intervention might influence some of these conditions. Two patients have had an exacerbation of their renal disease while on leptin therapy [12]. We have now observed a second patient with acquired generalised lipodystrophy who developed T cell lymphoma while on leptin replacement. Since T cell lymphoma has been reported in a patient with lipodystrophy [14], we do not know whether the lymphoma is a separate syndrome or whether it may have been affected by leptin treatment. Presently, we are cautious about the use of leptin in patients with acquired forms of lipodystrophy.

Leptin has been used to treat other features of lipodystrophy, such as steatohepatitis [27] and polycystic ovary syndrome [28, 29]. It has also been shown to have beneficial effects in congenital leptin deficiency, the Rabson–Mendenhall syndrome and functional hypothalamic amenorrhoea [30–33]. The discovery of leptin was truly seminal in demonstrating that adipose tissue is an important endocrine organ and plays a key role in regulating energy balance. Furthermore, leptin has provided an innovative approach to studying the neurobiology of energy regulation. We can now state that leptin has advanced from a laboratory discovery to a pharmaceutical product. It is the first novel therapy for extreme forms of insulin resistance since the discovery of insulin in 1921.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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