0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(7):3199–3207

doi: 10.1210/jc.2003-032140

Proteinuric Nephropathy in Acquired and Congenital Generalized Lipodystrophy: Baseline Characteristics and Course during Recombinant Leptin Therapy

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Generalized lipodystrophy is characterized by adipose tissue absence, hypoleptinemia, hypertriglyceridemia, insulin resistance, diabetes, hepatomegaly, and nonalcoholic steatohepatitis. In the course of recruiting patients for treatment with recombinant leptin, we were struck by the frequency and severity of proteinuria. We evaluated 25 patients with generalized lipodystrophy. Eighteen were treated with recombinant leptin, and we have followed 15 on leptin for 4–36 months. We followed renal parameters at baseline and during follow-up visits. Renal biopsies were performed as clinically indicated. At baseline, 22 of 25 patients (88%) had elevated urine albumin excretion (>30 mg/24 h), 15 (60%) had macroalbuminuria (>300 mg/24 h), and five (20%) had nephrotic-range proteinuria (>3500 mg/24 h). Twenty-three (92%) had elevated creatinine clearance (>125 ml/min·1.73 m^2). Eleven of 15 patients (73%) treated with recombinant leptin exhibited reduction in proteinuria, associated with reduction of hyperfiltration. Four patients who did not improve are discussed individually. Renal biopsy findings were remarkable for focal segmental glomerulosclerosis in four patients, membranoproliferative glomerulonephritis in two patients, and diabetic nephropathy in one patient. In conclusion, generalized lipodystrophy is associated with proteinuria and unique renal pathologies, including focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis. The majority treated with recombinant leptin demonstrated reduction in proteinuria and hyperfiltration. (*J Clin Endocrinol Metab* 89: 3199–3207, 2004)

ACQUIRED AND CONGENITAL generalized lipodystrophy syndromes are characterized by absence of body fat, low levels of the adipocyte-derived hormone/cytokine leptin, severe hypertriglyceridemia, insulin resistance associated with diabetes, hepatomegaly, and hepatic steatosis (1, 2). Although nephropathy has been previously reported (3–6), it has not been well characterized as a feature of these syndromes. By contrast, an acquired partial form of lipodystrophy has been associated with a higher frequency of membranoproliferative glomerulonephritis (MPGN) type 2, associated with a low C3 complement level in the presence of C3 nephritic factor (7–16).

In the course of assembling a group of patients for a clinical trial of recombinant leptin administration as a potential therapy for the metabolic and pituitary abnormalities of these syndromes (17, 18), we were struck by the extent of proteinuria exhibited. In the present study, we describe the types of renal diseases thus far elucidated that are associated with these generalized lipodystrophy syndromes. Further, we describe the renal parameters observed in patients who were treated with recombinant leptin over a period of up to 3 yr.

Abbreviations: AGL, Acquired generalized lipodystrophy; CGL, congenital generalized lipodystrophy; FSGS, focal segmental glomerulosclerosis; HbA1c, glycosylated hemoglobin; MPGN, membranoproliferative glomerulonephritis.

Patients and Methods

Patients

A total of 25 patients with generalized lipodystrophy are presented in this analysis. Seven patients have acquired generalized lipodystrophy (AGL), and 18 patients have congenital generalized lipodystrophy (CGL). The diagnosis of CGL was made clinically based on the presence of lipodystrophy within the first year of life. Patients who had normal fat tissue within the first year of life and subsequently developed generalized fat loss were classified as AGL. Body composition studies on these patients have demonstrated normal lean body mass despite low percent body fat (19). Fifteen patients were female, and 10 were male. They ranged in age from 8–67 yr.

All 25 patients had similar phenotypic features of lipodystrophy. Five patients were excluded because they did not meet entry requirements for the protocol (four due to inadequate metabolic abnormalities and one due to concurrent thyroid cancer), and two patients died while being considered for leptin therapy. The remaining 18 patients initiated recombinant leptin therapy in a protocol designed primarily to study the effects of leptin replacement on glycemic and lipid parameters (17). The study was approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases. Informed consent was obtained from the patient or his or her legal guardian. Fifteen of the 18 patients have been followed on recombinant leptin for at least 4 months. Leptin replacement therapy was given as a self-administered, twice-daily sc injection as previously described (17, 19). Patients were seen as inpatients every 4 months for the first year and then every 6 months thereafter. Renal parameters were measured during each visit.

Data were collected on a metabolic unit, including 24-h urine collections to ensure completeness. Diabetic and lipid medications were lowered or discontinued if indicated.

Biochemical analyses

Serum leptin levels were determined by immunoassays with the use of a commercial kit (Linco Research, St. Charles, MO) on samples drawn after an overnight fast. Glycosylated hemoglobin (HbA1c) values were measured by ion-exchange HPLC (Bio-Rad Laboratories, Hercules, CA). Serum creatinine and urine creatinine, albumin, and total protein were determined according to standard methods with the use of automated equipment (Beckman, Fullerton, CA). Creatinine clearance was calculated from serum and 24-h urine creatinine values [urine volume (ml) × urine creatinine (mg/dl)]/[time (1440 min) × serum creatinine (mg/dl)] and normalized for 1.73 m^2.

Renal biopsies

Routine percutaneous renal biopsies were not included in the original protocol but were performed as deemed clinically indicated for excessive or worsening proteinuria. Two biopsies (NIH-2 and NIH-25) were obtained by the patients' primary nephrologists before their initial National Institutes of Health (NIH) evaluations. Renal tissue was analyzed at autopsy in two cases (NIH-CGL1 and NIH-CGL3). Light microscopy samples were read by an experienced nephrologist at the NIH and reviewed by the Armed Forces Institute of Pathology, who carried out immunofluorescence and electron microscopy.

Results

Baseline clinical characteristics

Twenty-five patients with generalized forms of lipodystrophy were studied (Table 1). Eighteen patients had CGL, and seven patients had AGL. The median age of the patients was 18 yr (range, 8–67 yr). Resting blood pressures were less than 140/90 mm Hg for all adults and less than 95th percentile adjusted for age, height, and gender for children (20). Twenty of 25 patients had previously diagnosed diabetes, of which 19 had HbA1c more than 7% despite using a variety of medications. There were no consistent abnormalities of autoimmune and inflammatory markers at baseline or after leptin therapy.

Baseline renal parameters

The most common biochemical renal abnormality seen was proteinuria (Table 2 and Fig. 1). The median urinary albumin excretion was 644 mg/24 h (range, 7–9,461 mg/24 h). Twenty-two of 25 patients (88%) had elevated urinary albumin excretions (>30 mg/24 h), and 15 patients (60%) had macroalbuminuria (>300 mg/24 h). The median urinary protein excretion was 1120 mg/24 h (range, 191–11,365 mg/24 h), with 5 patients (20%) having nephrotic range proteinuria (>3,500 mg/24 h). The median protein/creatinine ratio was 0.58 (range, 0.08–13.65). The other notable finding was an elevation of creatinine clearance (Fig. 1), which we presume reflected marked hyperfiltration. The median creatinine clearance was 205 ml/min·1.73m^2 (range, 37–452 ml/min·1.73 m^2). All values of creatinine clearance, urine albumin, and urine protein were expressed both as raw data and normalized for 1.73 m^2 (Table 2).

One patient (NIH-CGL1) with CGL died of sudden cardiac death at age 30 during an inpatient evaluation at our clinical center before starting leptin. She had a history of diabetes since age 10 and had diabetic retinopathy. She was on insulin therapy and had a HbA1c level of 7.3%. Her serum creatinine

TABLE 1. Baseline clinical characteristics of patients

Patient no.[a]	Age (yr)	Sex	Type of lipodystrophy	Resting BP (mm Hg)	Serum leptin (ng/ml)[b]	HbA1c (%)	Autoimmune/ inflammatory markers[c]
NIH-1	17	F	AGL at age 12	116/79	1.5	8.0	None
NIH-2	17	F	CGL	133/74	2.5	9.8	ANA, ↑ ESR
NIH-3	27	F	AGL at age 3	109/67	1.7	9.3	↓ C4, Antismooth muscle
NIH-4	17	F	CGL	135/84	1.2	7.6	None
NIH-5	15	F	CGL	114/68	0.8	9.6	None
NIH-6	36	F	CGL	126/68	<0.5	9.5	↑ Anti-TPO
NIH-8	40	F	CGL	134/82	1.4	7.6	↑ ESR
NIH-9	13	F	AGL at age 6	122/63	4.0	10.6	↑ ESR
NIH-10	8	F	AGL at age 6	111/62	<0.5	5.9	↓ C4
NIH-11	13	M	CGL	109/76	1.3	9.3	ANA, ↑ ESR
NIH-13	12	F	CGL	101/63	0.8	7.2	↑ Anti-TG, ↑ Anti-TPO
NIH-14	35	M	AGL at age 3	107/61	1.1	9.5	↓ C3, C3NeF
NIH-15	67	M	AGL at age 63	114/70	0.5	8.1	None
NIH-19	30	F	AGL at age 28	118/74	1.3	8.0	C3NeF
NIH-20	23	F	CGL	101/56	1.4	8.7	None
NIH-22	15	F	CGL	112/55	3.3	13.0	None
NIH-24	18	M	CGL	115/65	0.9	10.2	None
NIH-25	15	F	CGL	134/72	2.1	11.0	↑ ESR, ↑ CRP
NIH-CGL1	30	F	CGL	134/76	1.7	7.3	↑ ESR
NIH-CGL2	19	M	CGL	117/67	<0.5	11.3	Anti-SmRNP
NIH-CGL3	31	M	CGL	106/50	0.5	4.8	None
NIH-CGL4	19	M	CGL	121/60	0.7	5.6	↑ Anti-TG
NIH-CGL5	17	M	CGL	101/56	0.9	3.7	None
NIH-CGL6	36	M	CGL	123/72	1.2	5.3	None
NIH-CGL7	11	M	CGL	126/67	2.5	4.8	ANA
Median	18	–	–	116/67	1.2	8.1	–

[a] NIH numbers correspond to previous publications (17, 19).
[b] Normal fasting range of leptin for males: 3.8 ± 1.8 ng/ml; females: 7.4 ± 3.7 ng/ml (33).
[c] ANA, Antinuclear antibody; Anti-SmRNP, antismith/ribonuclear protein; Anti-TG, antithyroglobulin; Anti-TPO, antithyroperoxidase; C3, complement 3; C3NeF, C3 nephritic factor; C4, complement 4; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

TABLE 2. Baseline renal parameters of patients

Patient no.	Serum creatinine (mg/dl)	Creatinine clearance		Urine albumin excretion		Urine protein excretion		Protein/ creatinine (mg/mg)	Using ACE or ARB
		(ml/min)	(ml/min/1.73 m^2)	(mg/24 h)	(mg/24 h/1.73 m^2)	(mg/24 h)	(mg/24 h/1.73 m^2)		
NIH-1	0.3	149	170	9461	10803	10099	11532	13.65	No
NIH-2	1.4	73	75	6426	6605	11365	11682	7.78	Yes
NIH-3	0.4	302	292	61	59	288	278	0.17	No
NIH-4	0.4	217	221	444	451	719	731	0.58	Yes
NIH-5	0.4	140	140	298	298	452	451	0.32	Yes
NIH-6	0.7	139	154	1488	1650	2616	2901	1.84	No
NIH-8	0.4	237	235	935	928	1366	1356	1.00	Yes
NIH-9	0.3	174	212	1831	2228	2675	3255	3.57	No
NIH-10	0.6	114	148	44	56	390	504	0.39	No
NIH-11	0.6	283	277	33	32	252	247	0.10	Yes
NIH-13	0.3	242	240	2130	2117	3295	3274	3.14	No
NIH-14	1.0	179	181	1452	1465	2450	2472	0.95	No
NIH-15	0.5	263	269	135	138	598	613	0.31	Yes
NIH-19	0.6	181	185	3544	3615	5160	5263	3.29	No
NIH-20	0.6	264	255	577	558	859	830	0.38	No
NIH-22	0.4	246	249	1901	1921	2925	2956	2.06	Yes
NIH-24	0.6	247	255	644	664	1120	1156	0.52	No
NIH-25	0.5	187	191	1868	1912	2737	2802	1.61	Yes
NIH-CGL1	1.4	33	37	2678	2969	3623	4017	5.49	No
NIH-CGL2	0.4	450	452	2628	2639	4368	4386	1.68	No
NIH-CGL3	0.6	216	214	14	14	172	170	0.09	No
NIH-CGL4	1.1	151	149	7	7	194	191	0.08	No
NIH-CGL5	0.7	217	205	19	18	191	181	0.09	No
NIH-CGL6	1.0	152	137	253	228	442	398	0.20	No
NIH-CGL7	0.7	110	128	167	194	342	397	0.31	No
Median	0.6	187	205	644	664	1120	1156	0.58	

ACE, Angiotensin-converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker.

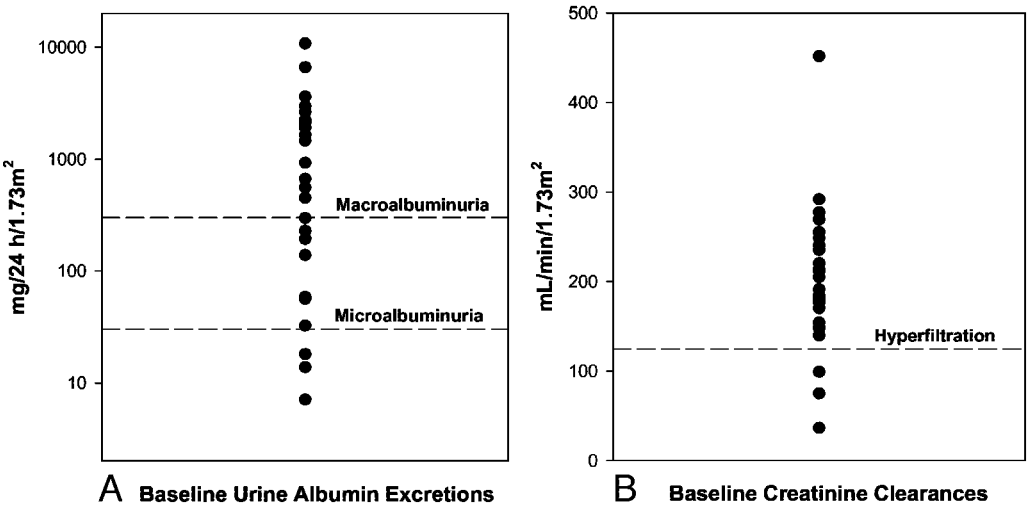

FIG. 1. Baseline albumin excretions (A) and creatinine clearances (B) of all patients evaluated with generalized lipodystrophy. The *dashed lines* correspond to abnormal thresholds as indicated.

was 1.4 mg/dl and creatinine clearance was markedly reduced (33 ml/min), with a urinary protein excretion of 3.6 g/24 h. At autopsy, her kidneys demonstrated typical diabetic nodular glomerulosclerosis (Fig. 2A).

Another patient (NIH-CGL3) died of idiopathic pulmonary fibrosis while being considered for compassionate leptin therapy. Autopsy did not reveal any renal abnormality.

Leptin therapy study

Fifteen patients entered an open-label therapeutic study of recombinant leptin for their severe insulin resistance, diabetes, dyslipidemia, and pituitary abnormalities and were observed for 4–36 months. Evidence for the efficacy of this therapy has been previously shown (17, 18). Along with improvements in the metabolic parameters (data not shown), 11 of 15 patients demonstrated a reduction in urinary protein excretion after 4 months of therapy that was maintained thereafter (Fig. 3). This was associated with a reduction in creatinine clearance, presumably reflecting reduction in glomerular hyperfiltration. The following four cases are of notable exception.

Patient NIH-9 (Fig. 4A) developed generalized lipodys-

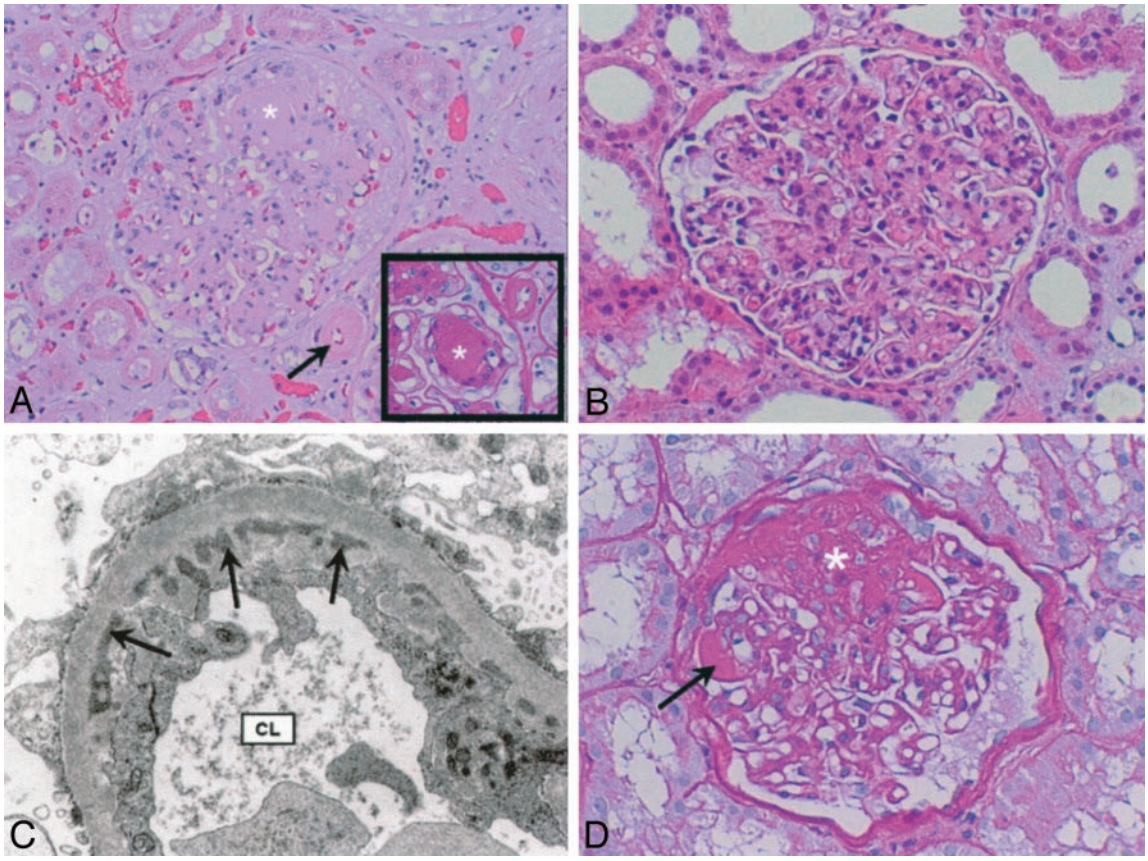

FIG. 2. Renal biopsies in patients with generalized lipodystrophy. A, Diabetic nodular glomerulosclerosis (hematoxylin and eosin stain). Typical hyaline deposits in the wall of an arteriole are indicated by the *black arrow*. Kimmelstiel-Wilson nodules are indicated by *white asterisks*, including the inset panel [periodic acid-Schiff (PAS) stain]. B, MPGN, type 1 (hematoxylin and eosin stain). The glomerulus shows endocapillary proliferation with compromise of capillary loop space. The mesangial matrix is expanded to give the glomerulus a lobulated appearance. C, MPGN (electron microscopy appearance of the same case presented in B). The glomerular wall surrounding the capillary lumen (CL) is thickened by extension of mesangial matrix and electron dense deposits (*black arrows*) in the subendothelial space. The micrograph was provided courtesy of Dr. Sharda Sabnis, Chief of the Nephropathology Section, Armed Forces Institute of Pathology, Washington, DC. D, Focal FSGS with hyalinosis (PAS stain). The segmental sclerosis is marked by the *white asterisk*. Segmental hyalinosis is marked by the *black arrow*.

trophy at age 6 yr in association with type 1 diabetes (low C-peptide and positive islet cell antibody). Over the next few years, she had progressive hypertriglyceridemia and hepatomegaly with evidence of nonalcoholic steatohepatitis. At age 13 yr, she was enrolled into the leptin therapy protocol. Her urinary protein was 2.8 g/24 h with normal serum creatinine and elevated creatinine clearance. She had elevated transaminases and a liver biopsy consistent with autoimmune hepatitis (data not shown) but normal complement levels and undetectable C3 nephritic factor. She was treated with leptin for 1 yr with a decrease in urine protein excretion to 1.5 g/24 h. Her renal function remained normal, her diabetes control improved, and her triglycerides began to fall. However, over the next 2 months, her bilirubin and transaminases began to rise and her albumin was noted to be very low. On readmission, she was found to have massive proteinuria of over 15 g/24 h. Renal biopsy revealed MPGN type 1 (Fig. 2, B and C). Leptin therapy was discontinued; but over the ensuing 8 months, her massive proteinuria persisted, and her renal function declined.

Patient NIH-14 (Fig. 4B) is a 35-yr-old male who developed total lipodystrophy around age 3 yr. When first seen at NIH, his urinary protein excretion was 2.5 g/24 h, and his creatinine clearance was 179 ml/min. Serum BUN and creatinine were normal. He had low C3 with positive C3 nephritic factor. After approximately 6 months of leptin therapy, he developed increased proteinuria, and his serum creatinine began to increase. Leptin therapy was discontinued at 8 months, and a renal biopsy was obtained, demonstrating MPGN type 1. Six months after discontinuing leptin, his proteinuria and elevated serum creatinine have worsened.

Patient NIH-2 (Fig. 4C) is a 17-yr-old female with CGL. She had a baseline urinary protein excretion of 11 g/24 h and a creatinine clearance of 73 ml/min. She was known to have proteinuria since age 11 yr, and a kidney biopsy done 2 yr before initiating leptin therapy revealed focal segmental glomerulosclerosis (FSGS). She was treated with leptin over an 18-month period during which she had a slow, but progressive, deterioration of renal function. There was an initial fall in urinary protein excretion that was not sustained. Leptin therapy was discontinued after 30 months as she approached end-stage renal disease.

Patient NIH-13 (Fig. 4D) was first seen at NIH at age 12 with CGL. She had a urinary protein excretion of 3.3 g/24 h and a creatinine clearance of 242 ml/min. Because of continued nephrotic range proteinuria after 12 months of leptin

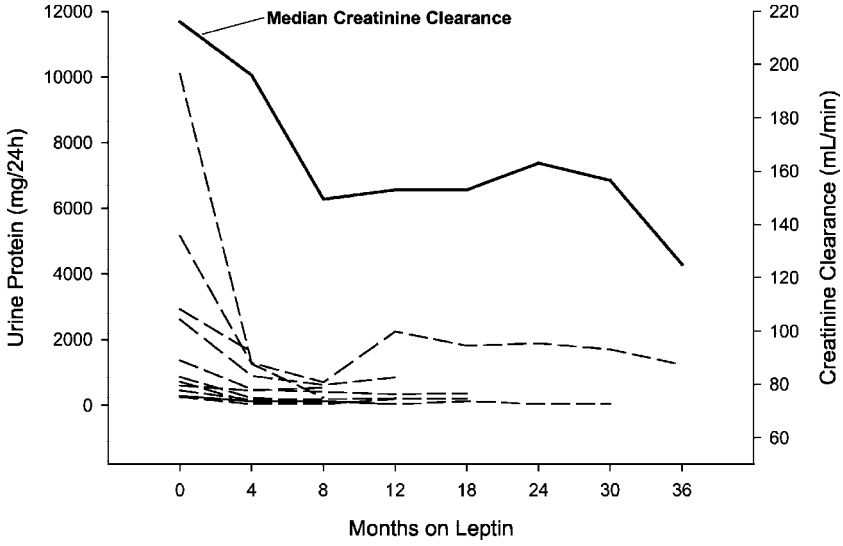

FIG. 3. Urine protein excretions in conjunction with median creatinine clearance of 11 patients treated with recombinant leptin for up to 36 months. The *dashed lines* correspond to individual urine protein excretions over time. The *solid line* corresponds to median creatinine clearance over time. The reduction in urine protein excretions in these patients from baseline to 4 months was significant ($P < 0.001$ by Wilcoxon signed-rank analysis). This graph does not include the patients discussed individually who are presented in Fig. 4.

therapy, she had a kidney biopsy, which revealed FSGS (Fig. 2D). She has now been followed for 16 months on leptin therapy and continues to have the same heavy proteinuria but normal renal function. Leptin therapy has been continued.

Renal biopsy results

We analyzed renal tissue from eight patients (Tables 3 and 4). Six patients had percutaneous biopsies obtained secondary to excessive proteinuria. Of these patients, all three with CGL demonstrated FSGS. Of the patients with AGL, one had FSGS and two had MPGN type 1. The renal tissue analysis of two patients done in conjunction with autopsies revealed diabetic nodular glomerulosclerosis in one and no abnormality in the other.

Discussion

We evaluated renal function and pathology in a group of patients with generalized lipodystrophy during the course of a therapeutic trial with recombinant human leptin. Of the 25 patients in this study with generalized forms of lipodystrophy, baseline evaluations demonstrated 88% with at least microalbuminuria (>30 mg/24 h), 60% with macroalbuminuria (>300 mg/24 h), and 20% with nephrotic range proteinuria (>3500 mg/24 h). One underlying risk factor that may have explained this clinical picture is longstanding poorly controlled diabetes. However, we documented diabetic nephropathy as the predominant feature of proteinuria in only one patient. It is possible that other patients who were not biopsied had diabetic nephropathy, but the major unexpected finding was the prevalence of other renal diseases that were documented, namely MPGN and FSGS. Both patients with MPGN had microscopic hematuria, but this was also seen in seven other patients (overall prevalence of 36%) in the presence and absence of other etiologic forms of nephropathies.

The primary purpose of this protocol was to follow metabolic changes in patients with generalized lipodystrophy treated with recombinant leptin. It was only through following this group of patients for 3 yr that we recognized the extent of underlying proteinuria, elevation of creatinine clearance, and renal pathology. We therefore do not have direct measurements of glomerular filtration rate. Although creatinine clearance is not identical to glomerular filtration rate, it has been widely used as its surrogate.

Textbooks of medicine and nephrology describe the relationship between an acquired form of partial lipodystrophy and MPGN type 2 (dense deposit disease), associated with low C3 and elevated C3 nephritic factor. These descriptions are based on numerous case reports (7–16). In fact, C3 nephritic factor has been implicated as a possible cause for partial lipodystrophy (8).

In contrast, the renal lesion(s) associated with generalized forms of lipodystrophy (congenital or acquired) has remained largely unknown. Forty years ago, Senior and Gellis (3) mentioned proteinuria in two patients with generalized lipodystrophy, but again most of the emphasis was on partial lipodystrophy and renal disease. Three case reports have mentioned diabetes, glomerulosclerosis, and glomerular lipid infiltration in association with generalized lipodystrophy (two congenital, one acquired) (4–6), and again we were surprised that we could not implicate glomerular lipid infiltration as etiologically related to the renal disease of our patients. This is despite the fact that many of the patients had marked elevation of serum triglyceride levels. Two patients (NIH-1 and NIH-9) had sparsely scattered lipid-ladened macrophages in a minority of glomeruli, unlikely to be pathogenetically relevant to the glomerular proteinuria.

Fifteen of the 25 patients in whom we report baseline data were further followed in a protocol using recombinant leptin to treat their metabolic disorders. We have reported initial results in ameliorating metabolic parameters, including insulin resistance, hyperglycemia, hypertriglyceridemia, and hepatic steatosis (17). We found marked elevation in creatinine clearance, which we interpret as renal hyperfiltration in conjunction with poorly controlled diabetes. In previous studies of obesity or congenital leptin deficiency (17–19, 21–26), there has been no mention of renal disease with leptin

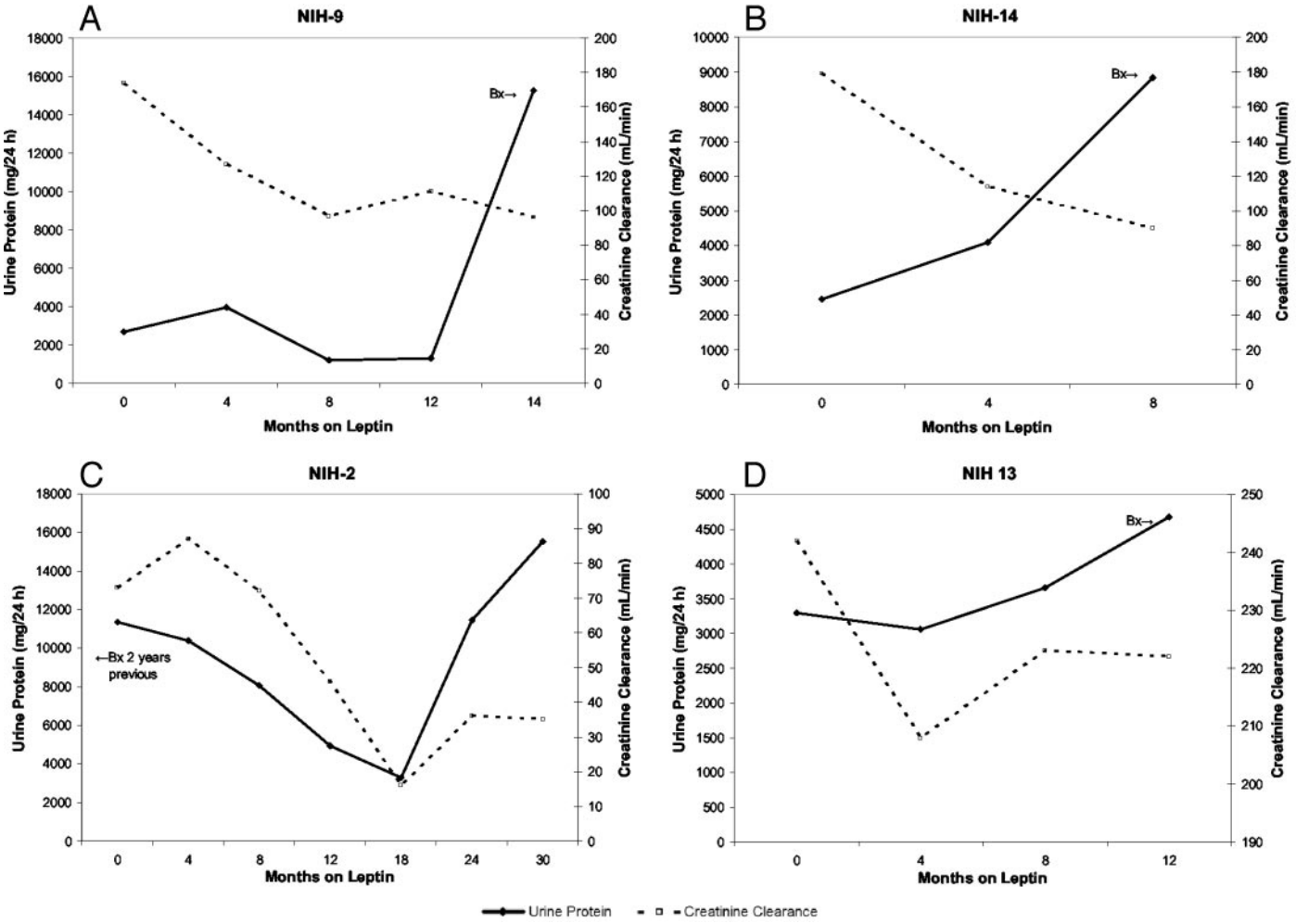

FIG. 4. Individual urine protein excretions and creatinine clearances over time while using recombinant leptin. The *solid lines* correspond to urine protein excretions over time. The *dashed lines* correspond to creatinine clearances over time. Renal biopsies (Bx) were performed as indicated. These values are separate from those in Fig. 3 and correspond to individual descriptions in the text.

TABLE 3. Clinical parameters at time of renal biopsy

Patient no.	Age (yr)	Sex	Type of lipodystrophy	Indication for biopsy	Serum creatinine (mg/dl)	Urine RBC/HPF	Urine protein (mg/24 h)
NIH-1	15	F	AGL at age 12	Proteinuria	0.2	Rare	2,202
NIH-2	14	F	CGL	Proteinuria	Unavailable	Unavailable	Unavailable
NIH-9	14	F	AGL at age 6	Proteinuria	0.6	11–20	15,788
NIH-13	13	F	CGL	Proteinuria	0.5	0	4,677
NIH-14	35	M	AGL at age 3	Proteinuria	2.0	>40	10,558
NIH-25	15	F	CGL	Proteinuria	0.5	0	2,737
NIH-CGL1	30	F	CGL	Autopsy	1.4	11–20	3,623
NIH-CGL3	31	M	CGL	Autopsy	0.6	21–40	172

RBC/HPF, Red blood cells per high-powered field.

therapy. In 11 of 15 patients, there was a reduction in proteinuria that coincided with a reduction in creatinine clearance and hence correction of hyperfiltration as a function of leptin therapy.

The other four patients who had a different course are of special note. In two patients with nephrotic range proteinuria at baseline and FSGS, one (NIH-13) remained stable at 1 yr of leptin therapy, and leptin has been continued, whereas the other (NIH-2) progressed toward end-stage renal disease. We assume that the renal disease in these two cases is unrelated to leptin therapy. In the two cases with MPGN, the issue is more complex. Both patients had heavy proteinuria at baseline. One patient (NIH-14) had low C3 with elevated C3 nephritic factor, whereas the other (NIH-9) had a different but strong autoimmune diathesis, including type 1 diabetes. These two patients with underlying renal disease had a marked exacerbation of their renal disease at 6 and 14 months of leptin therapy and no improvement after 6 and 9 months of discontinuing leptin. Thus, in these two patients who had underlying renal disease, we cannot exclude the possibility

TABLE 4. Renal biopsy data

Patient	Diagnosis	Light microscopy	Fluorescence microscopy	Electron microscopy
NIH-1	FSGS	Normal glomerular cellularity; rare focal, segmental sclerotic lesions; foam cells in some glomerular capillaries; minimal tubular atrophy and interstitial fibrosis; no arteriolar hyalinosis	No glomeruli in tissue sample	Normal thickness GBM; foam cells in capillary lumina; no effacement of podocyte foot processes; no electron-dense deposits
NIH-2	FSGS	Normal glomerular cellularity; focal, segmental sclerotic lesions with adjacent adhesions to Bowman's capsule; mild focal chronic inflammation, tubular atrophy and interstitial fibrosis; no arteriolar hyalinosis	Glomerular mesangium: IgG (−); IgA (−); IgM (1 + focal); C3 (−)	Focal effacement of podocyte foot processes; no electron-dense deposits
NIH-9	MPGN Type 1	Diffuse endocapillary proliferation (lobular pattern) with focal double contours; no crescents or necrosis; moderate focal chronic inflammation, tubular atrophy and interstitial fibrosis; no arteriolar hyalinosis	No glomeruli in tissue sample	Thickened GBM; subendothelial mesangial interposition (double contours); numerous mesangial and subendothelial deposits; rare subepithelial deposits; extensive effacement of podocyte foot processes
NIH-13	FSGS	One fourth obsolescent glomeruli; normal glomerular cellularity; focal, segmental sclerotic lesions with hyalinosis and adhesions to Bowman's capsule; moderate focal chronic inflammation; mild tubular atrophy and interstitial fibrosis; no arteriolar hyalinosis	Glomerular mesangium: IgG (−); IgA (−); IgM (2+); C3 (−); C1q (−)	Irregular mesangial expansion; no electron-dense deposits; focal effacement of podocyte foot processes
NIH-14	MPGN Type 1	One third obsolescent glomeruli; diffuse endocapillary proliferation (lobular pattern) with focal double contours; no crescents or necrosis; mild focal chronic inflammation, tubular atrophy, and interstitial fibrosis; no arteriolar hyalinosis	Glomerular capillary loops: IgG (1+); IgA (−); IgM (3+); C3 (3+); C1q (3+)	Irregular thickening of GBM; mesangial expansion with irregular subendothelial interposition (double contours); moderate mesangial, subendothelial and intramembranous deposits; extensive effacement of podocyte foot processes
NIH-25	FSGS	Normal glomerular cellularity; focal, segmental sclerotic lesions with a variable mix of overlying visceral epithelial hyperplasia and adhesions to Bowman's capsule; minimal tubular atrophy; no arteriolar hyalinosis	Glomerular mesangium: IgG (−); IgA (−), IgM (3+ focal, segmental); C3 (−)	Irregular mesangial expansion; no electron-dense deposits; focal effacement of podocyte foot processes
NIH-CGL1	DN (autopsy)	More than 50% obsolescent glomeruli; viable glomeruli: marked mesangial expansion with sclerotic nodules (Kimmelsteil-Wilson lesions); focal, segmental fibrin caps and capsular drops; hyalinosis of arterioles; moderate chronic inflammation, tubular atrophy and interstitial fibrosis	ND	ND
NIH-CGL3	Non-diagnostic (autopsy)	Less than 10% obsolescent glomeruli; viable glomeruli: focal tuft retraction but no definitive or discrete sclerotic lesions; mild focal tubular atrophy and interstitial fibrosis; no arteriolar hyalinosis	ND	ND

DN, Diabetic nephropathy; GBM, glomerular basement membrane; ND, not done.

that leptin therapy was associated with exacerbation of their underlying renal disease.

An additional patient with CGL, not included in this report, had end-stage renal disease of unknown etiology at presentation. She underwent a renal transplant and is the subject of a separate report (27). Leptin therapy was initiated 1 yr after the transplant, and she continues to do well after 1 yr on recombinant leptin therapy.

The association between leptin and renal abnormalities has been investigated using various rodent models. One model studied leptin's ability to increase expression of TGF-β. Wolf *et al.* (28) demonstrated increased expression of TGF-β1 in cultured rat glomerular endothelial cells incubated with leptin, as well as increased proteinuria and glomerulosclerosis in naïve rats administered leptin for 3 wk. Although leptin administration may be associated with increased TGF-β and renal disease in rodents, it is yet unclear what relevance it may have in human studies. The above authors suggest that the increased incidence of glomerulosclerosis observed in obese patients in the setting of elevated leptin levels may involve increased expression of TGF-β. Although FSGS was identified in four of our patients, this hypothesis fails to account for two patients diagnosed with FSGS before receiving leptin (NIH-2 and NIH-25). Additional patients with generalized lipodystrophy diagnosed with forms of glomerulosclerosis (4–6) had also never received leptin.

Nevertheless, TGF-β is an intriguing theory in the development of renal disease, particularly FSGS. To be the cause of FSGS in patients with lipodystrophy, increased TGF-β activity would presumably need to exist before leptin replacement. Whether lipodystrophy is a state of increased TGF-β activity has not been established. A rodent model suggests that TGF-β may not only be associated with renal disease but may even be involved in the development of lipodystrophy itself. Transgenic mice designed to overexpress TGF-β1 in adipose, renal, and hepatic tissues developed lipodystrophy, glomerulosclerosis, and cirrhosis with variable penetrance (29). Ultimately, the roles of TGF-β in human disease should be further explored.

Another rodent model examined leptin's role in modulating the immune system. Sanna *et al.* (30) demonstrated a clear link between leptin presence and onset of experimental autoimmune encephalitis, a Th1-mediated disease, in susceptible mice. *Ob/ob* mice deficient in leptin were protected against this condition. This was reversed with leptin replacement. Again, the relevance of these rodent studies to the human condition is unclear. Limited data in children with congenital leptin deficiency showed a reduction in $CD4^+$ T cell count that was restored to normal after leptin treatment (23). This was associated with a more robust cytokine response to various *in vitro* stimuli. Whether leptin replacement can lead to pathological $CD4^+$ activity through Th1 lymphocytes in humans is speculative.

We have described a variety of renal pathologies associated with proteinuria in patients with generalized lipodystrophy. We were surprised by the lack of predominating diabetic nephropathy, despite the prevalence of diabetes and proteinuria. Instead, we identified two distinct pathologies usually associated with other illnesses. The major finding in patients with CGL was FSGS with the exception of one patient with diabetic nephropathy. One patient with AGL (NIH-1) also had FSGS. However, two patients with AGL had MPGN type 1, which has not been previously reported. In contrast, acquired partial lipodystrophy has been associated with MPGN type 2, low C3, and elevated C3-nephritic factor. Only one of the two patients with AGL and MPGN (NIH-14) had this abnormal complement profile. At this point, it is certainly premature to predict renal pathology based on the type of generalized lipodystrophy. Yet, renal disease is clearly a significant component of generalized lipodystrophy. We are unable, however, to provide a mechanistic link for either of these divergent processes. The acquired forms may have an autoimmune basis, but the congenital forms are associated with at least two different genetic mutations (31, 32). Whether these processes have any relevance to the various rodent models of TGF-β or immune dysfunction remains speculative.

Leptin is a cytokine that is decreased in lipodystrophy, but there are no models to suggest how a deficiency of leptin or any of the other known adipokines may be related to renal disease. Whether physiological replacement could lead to an exacerbation of underlying renal disease in patients, whose metabolic parameters improve on recombinant leptin therapy, remains an important question.

Note Added in Proof

Since the time of submission, we have seen an additional 17-yr-old female with CGL and biopsy-proven FSGS prior to starting leptin. Baseline values included 24-h urine protein of 2618 mg/dl and creatinine clearance of 163 ml/min.

Acknowledgments

Received December 15, 2003. Accepted March 29, 2004.

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