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Renal Complications of Lipodystrophy: a closer look at the natural history of kidney disease

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Abstract

Objectives—Lipodystrophy syndromes are a group of heterogeneous disorders characterized by adipose tissue loss. Proteinuria is a remarkable finding in previous reports.

Study design—In this multi-center study, prospective follow-up data were collected from 103 subjects with non-HIV associated lipodystrophy registered in the Turkish Lipodystrophy Study Group database to study renal complications in treatment naïve patients with lipodystrophy.

Methods—Main outcome measures included ascertainment of chronic kidney disease (CKD) by studying the level of proteinuria and the estimated glomerular filtration rate (eGFR). Kidney volume was measured. Percutaneous renal biopsies were performed in 9 patients.

Results—Seventeen of 37 patients with generalized and 29 of 66 patients with partial lipodystrophy had CKD characterized by proteinuria, of those 12 progressed to renal failure subsequently. The onset of renal complications was significantly earlier in patients with generalized lipodystrophy. Patients with CKD were older and more insulin resistant and had worse metabolic control. Increased kidney volume was associated with poor metabolic control and suppressed leptin levels. Renal biopsies revealed thickening of glomerular basal membranes, mesangial matrix abnormalities, podocyte injury, focal segmental sclerosis, ischemic changes and tubular abnormalities at various levels. Lipid vacuoles were visualized in electron microscopy images.

Conclusions—CKD is conspicuously frequent in patients with lipodystrophy which has an early onset. Renal involvement appears multifactorial. While poorly controlled diabetes caused by severe insulin resistance may drive the disease in some cases, inherent underlying genetic defects may also lead to cell-autonomous mechanisms contributory to the pathogenesis of kidney disease.

Keywords

Lipodystrophy; proteinuria; chronic kidney disease; insulin resistance

Introduction

Lipodystrophy syndromes are a group of heterogeneous disorders affecting adipose tissue differentiation or distribution as well as metabolism. Congenital generalized lipodystrophy (CGL) is a rare, mostly autosomal recessive disorder characterized by near total absence of the body adipose tissue. Several genes have been identified for CGL which includes 1-acylglycerol-3-phosphate O-acyltransferase 2 *(AGPAT2)*, Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*), caveolin 1 *(CAV1)* and polymerase I and transcript release factor *(PTRF)* [1]. The lack of adipose tissue is selective in patients with partial lipodystrophy. Mutations in several genes have been identified in different subtypes of familial partial lipodystrophy (FPLD), most of which are inherited as an autosomal dominant trait. The most common subtype of FPLD, FPLD2 is caused by heterozygous mutations in the lamin A/C (*LMNA*) gene [2]. In acquired lipodystrophy syndromes, patients develop adipose tissue loss at some point during life [3].

The kidney is one of the organs affected in lipodystrophy. The etiologic basis of renal complications associated with lipodystrophy has remained largely unknown; however, it is usually characterized by proteinuria [4]. Javor et al. [5] reported that proteinuria was strikingly frequent in patients with generalized lipodystrophy who were being treated with metreleptin. Renal involvement has also been reported in the course of FPLD [6–8]. Renal involvement in acquired partial lipodystrophy (APL) has been associated with abnormalities of the alternative complement pathway, which is C3-nephritic factor associated mesangiocapillary glomerulonephritis (C3-MPGN) [3].

Considering that novel treatments are in progress in lipodystrophy, it is essential to document the natural history of the disease and the disease burden in patients with lipodystrophy who are naïve to these lipodystrophy specific novel treatments. In this multicenter observational study, we specifically focused on renal complications. We studied 103 novel drug naïve patients with various forms of lipodystrophy for renal abnormalities who were registered in the Turkish Lipodystrophy Study Group (TuLip) national registry. To better understand the pathogenesis of renal involvement in patients with lipodystrophy, we further investigated the renal biopsy samples of 9 patients.

Materials and Methods

Patients

Initially, 109 patients with non-HIV associated lipodystrophy from the TuLip registry were included in this study. None of the patients received metreleptin or any other drug in development for lipodystrophy at the time of data collection. Patients with specific syndromes such as mandibuloacral dysplasia, Short syndrome and Candle/JMP syndrome were excluded from the study. Five patients were not included in the analysis as they either did not have a regular follow-up for renal complications or refused to attend the data collection visits. Another patient with partial lipodystrophy was excluded as he was diagnosed with systemic lupus erythematosus, and lupus nephritis was detected on the renal biopsy. The study was approved by the Dokuz Eylul University Ethics Review Panel. Written informed consent was obtained.

Diagnosis and classification of lipodystrophy

CGL was diagnosed based on generalized adipose tissue loss that was remarkable at birth or noticed at early stages of life. Acquired generalized lipodystrophy (AGL) was diagnosed based on the development of generalized adipose tissue loss later on in childhood or later. FPLD was diagnosed based on partial adipose tissue loss in selected areas. APL was diagnosed based on acquired adipose tissue loss characteristically starting at the face, progressing in a cephalocaudal fashion to the trunk and upper extremities. Adipose tissue distribution was also assessed by whole-body magnetic resonance imaging (WB MRI; Gyroscan Intera, release 8.1; Philips Medical Systems, Best, the Netherlands) with a 6-multichannel body coil. Mutation analysis of the genes *LMNA, LMNB2, PPARG, AGPAT2, BSCL2, CAV1, PTRF, PLIN1, AKT2, LIPE, ADRA2A, ZMPSTE24*, and *CIDEC* was carried out by direct automated DNA sequencing from the patients' genomic DNA, based on the clinical features. Sequencing was performed with Miseq V2 chemistry on MiSeq instrument (Illumina, California, USA).

Data collection and analysis

The prospective follow-up data were collected by the investigators at several centers of the TuLip. After reviewing the registry retrospectively, a final visit was scheduled to update the clinical findings. Blood pressure was measured using a sphygmomanometer in the sitting position after 5 minutes rest. For the adult age group, patients on antihypertensive treatment and those with resting blood pressure higher than 140/90 mm Hg were considered as hypertensive. For the pediatric age group, adjusted blood pressure for age, height and gender higher than 95^{th} percentile was considered as having hypertension.

Patients underwent a detailed physical examination, full biochemistry and urinalysis for protein content. Biochemical tests were studied by standardized methods with appropriate quality control and quality assurance procedures. Direct low-density lipoprotein (LDL) cholesterol measurement was performed. Leptin and adiponectin levels were measured with enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Boster, Pleasanton, CA, USA). Diabetes was defined according to the recommendations of American Diabetes Association (ADA) [9]. Lipid levels were classified according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guidelines [10]. Age-specific thresholds were used for children and adolescents [11].

We defined chronic kidney disease (CKD) as abnormalities of kidney structure or function, which persisted for at least 3 months. Estimated GFR (eGFR) was calculated using the CKD-EPI formula [12]. Bedside Schwartz formula was used for children [13]. eGFR and proteinuria were classified according to the Kidney Disease Outcomes Quality Initiative (KDOQI) and updated guideline of the Kidney Disease Improving Global Outcomes (KDIGO) [14]. The screening strategy for albuminuria/proteinuria consisted of urine dipstick test, spot urine protein/creatinine test, spot urine albumin/creatinine ratio and 24-h urine collections. We were able to perform 24-h urine collections in 100 of 103 patients. Positive dipstick test results were followed by a quantitative measurement. In adults (≥ 18 years), urinary protein excretion of ≥ 150 mg/day was considered to be abnormal. Microalbuminuria (moderately increased albuminuria) was diagnosed from a 24-hour urine

collection (between 30–300 mg/day) or from a spot sample (30 – 300 mg/g). Macroalbuminuria (severely increased albuminuria) was defined as an albumin excretion ≥ 300 mg/day or ≥ 300 mg/g on a spot specimen. Nephrotic-range proteinuria was considered with a protein excretion of 3.5 grams or more per day. Proteinuria in children was defined as greater than 100 mg/m^2 urinary protein excreted per day. On a spot urine protein/creatinine test, proteinuria was defined as a ratio >0.2 in children older than 2 years of age or a ratio >0.5 in children aged between 6–24 months old [15]. Nephrotic range proteinuria in children was defined as urinary protein excretion that exceeded 40 mg/m^2/hour. We considered eGFR levels less than 60 ml/min/1.73 m^2 as "decreased." In those with an eGFR ≥ 60 ml/min/1.73 m^2, the presence of proteinuria established the diagnosis of CKD. End-stage renal disease (ESRD) was defined as having an eGFR less than 15 mL/min/1.73m^2. Elevated eGFR, which may reflect hyperfiltration, was considered if eGFR exceeded 130 ml/min/1.73 m^2 in adults and 150 ml/min/1.73 m^2 in children.

Measurement of kidney volumes

Kidney morphology was studied on either ultrasound or MRI. Kidney volumes were measured on axial 3D GRE fat saturated T1 weighted MRI images (Achieva 1.5-T scanner, Philips Medical Systems, Best, the Netherlands) using Myrian software (IDS 2.0, Sectra AB, Sweden). The interpretation of the measurements was done as suggested by Cheong et al [16].

Renal biopsy

Percutaneous renal biopsies were performed in 9 patients. All patients had proteinuria and insulin resistant diabetes. Samples were stained with hematoxylin and eosin (HE), periodic acid-Schiff (PAS), periodic acid methenamine silver (PAM) stains and Congo-red in 2–3 micron sections. For immune deposits, each specimen was evaluated using antibodies against IgG, IgA, IgM, complement-3 (C3), complement-1q (C1q), kappa and lambda. Light microscopy, immunofluorescence and electron microscopy (EM) samples were read by three experienced pathologists.

Statistical analysis

Statistical analysis was performed using Statistical Package of Social Science (SPSS Inc, Chicago, IL, USA), version 22 for Windows. Student's t-test or Mann Whitney U test was used for comparison of scale parameters depending on distribution of variables. Categorical variables were compared by the chi-square test. The Spearman rank correlation coefficient was used to determine the relationship existing between continuous parameters. Partial correlations method was also used to measure the association between two variables while controlling the effect of additional variables. A p-value less than 0.05 was accepted as statistically significant.

Results

The GL and PL cohorts were previously reported to describe mostly metabolic abnormalities [17, 18]. The age was heterogeneous ranging from 1 to 77 years. Thirty-seven patients had generalized lipodystrophy, of those 34 had CGL. CGL was caused by *AGPAT2* mutations in

19 patients, *BSCL2* mutations in 13 patients, and *PTRF* mutations in 2 patients. Three patients had AGL. Sixty-six patients had partial lipodystrophy. Of those, 44 patients had FPLD. FPLD was caused by *LMNA* mutations in 21 patients, and *PPARG* mutations in 9 patients. We were not able to detect any pathogenic variant in 14 patients with FPLD in the genes sequenced. Twenty-two patients had APL.

Seventeen of 37 patients (46%) with generalized lipodystrophy developed CKD characterized by proteinuria. CKD was present in all patients with CGL older than 26 years. The onset of renal complications was significantly earlier in patients with generalized lipodystrophy compared to those with FPLD (Table-1). Patients with generalized lipodystrophy were younger and they were more insulin resistant although they had lower BMI. Hepatic steatosis was more severe (imaging data not shown here). Patients with generalized lipodystrophy had significantly lower levels of leptin and adiponectin (Table-1). Proteinuria was almost two times more common than retinopathy in patients with generalized lipodystrophy (Suppl. Table-1). Proteinuria was at nephrotic range in 5 patients (14%). Also, 10 additional patients (27%) with generalized lipodystrophy had hyperfiltration. Eight patients (22%) with generalized lipodystrophy had decreased eGFR. Of those, ESRD was detected in four patients (11%). Three patients required hemodialysis. A patient with CGL was successfully treated with continuous ambulatory peritoneal dialysis (CAPD) for a year, then she underwent a successful renal transplant.

Twenty-nine patients (44%) with partial lipodystrophy developed CKD associated with proteinuria (Suppl. Table-2). Three patients (5%) had proteinuria at nephrotic range. Five patients (8%) had hyperfiltration. Four patients (6%) with partial lipodystrophy had a progressive decrease in eGFR. Among them, a patient with APL developed ESRD, who was treated with hemodialysis. She received a successful renal transplant later. Serum C3 levels were suppressed in 12 of 22 (55%) patients with APL, although no patient with FPLD had C3 levels below reference values (APL vs. FPLD: 56 ± 39 mg/dL vs. 142 ± 24 mg/dL, $p < 0.001$). In the whole study group, patients who developed CKD were older and had more severe insulin resistance. Diabetes and lipids were poorly controlled. CKD was accompanied by hypertension in more than half of the patients (Suppl. Table-3). There was only one patient with GL who developed CKD before the appearance of diabetes in the whole registry when patients with APL were excluded. However, 15 of 81 patients (19%) developed CKD before or within 5 years of diabetes diagnosis, which was far earlier than general diabetes population [19].

Kidney volumes were measured in 48 patients [15 with generalized lipodystrophy (14 CGL and 1 AGL), and 33 with partial lipodystrophy (25 FPLD and 8 APL)] on MRI. Nephromegaly was observed in 26 patients (54.2%), of those 10 had CGL, 1 AGL, 13 FPLD and 2 APL. Kidney volumes were significantly elevated in patients generalized lipodystrophy compared to those with partial lipodystrophy (312 ± 116 cm^3 vs. 223 ± 48 cm^3, $p = 0.012$ for the left kidney; 285 ± 94 cm^3 vs. 216 ± 49 cm^3, $p = 0.016$ for the right kidney). Kidney volumes were found to be positively correlated with fasting glucose ($r = 0.602$, $p < 0.001$ for the left kidney, Fig. 1a; $r = 0.499$, $p = 0.002$ for the right kidney, Fig. 1b), HOMA-IR score ($r = 0.435$, $p = 0.007$ for the left kidney, Fig. 1c; $r = 0.349$, $p = 0.034$ for the right kidney, Fig. 1d) and HbA1c ($r = 0.75$, $p < 0.001$ for the left kidney; Fig. 1e, r =

0.693, $p < 0.001$ for the right kidney, Fig. 1f); and negatively correlated with leptin levels [$r = -0.295$, $p = 0.076$ (not statistically significant) for the left kidney; Fig. 1g, $r = -0.385$, $p = 0.019$ for the right kidney, Fig. 1h], when the data were controlled for age, gender, BMI and eGFR.

Table-2 summarizes the results of percutaneous renal biopsies and the clinical features of patients at the time of the biopsy. Renal biopsy was performed in 4 patients with generalized lipodystrophy (3 patients with CGL caused by *AGPAT2* mutations and 1 patient with AGL). Glomerular basal membranes (GBMs) were thickened in all patients with generalized lipodystrophy (Fig. 2a). Mesangial expansion was remarkable (Fig. 2b). Podocyte injury was obvious (Fig. 2c). Areas of focal segmental sclerosis (FSGS) were observed (Fig. 2b). Ischemic changes were detected at various levels such as wrinkled GBMs and glomerular shrinkage (Fig. 2d). Lipid vacuoles were visualized on EM images (Fig. 2c). Renal biopsy was performed in 5 patients with partial lipodystrophy. Renal biopsy showed (Fig. 2e) marked mesangial expansion with Kimmelstiel-Wilson nodules in a patient with FPLD caused by an *LMNA* pathogenic variant (R482W). GBMs were thickened. Ischemic changes were remarkable. Podocyte injury and FSGS were detected (Fig. 2f). Another biopsy from a patient with FPLD caused by a *PPARG* pathogenic variant revealed similar findings at different levels, but also IgA deposits in immunofluorescence microscopy which probably could be a coincidental pathology. Renal biopsy was performed in two sisters with mutation negative FPLD which showed ischemic changes such as irregular thickening and wrinkling of the GBM, small areas of FSGS and podocyte foot process effacement. Renal biopsy was performed in a diabetic APL patient with low levels of circulating C3 which showed mesangial expansion and hypercellularity, thickening of GBMs and podocyte injury. Lipid vacuoles were visualized on EM images.

Discussion

Although the kidney is one of the organs reported to be affected in the course of generalized lipodystrophy, the pathophysiology of renal damage has not been studied in a systematic fashion. In a previous study, Javor et al. [5] reported elevated urine albumin excretion in 22 of 25 (88%) patients with generalized lipodystrophy, of those 15 (60%) had macroalbuminuria, and 5 (20%) had nephrotic range proteinuria. Although proteinuria was also remarkably prevalent in our generalized lipodystrophy registry (35% with macroalbuminuria and 14% with nephrotic range proteinuria), our observed range was significantly lower. This may be because some patients were very young or recently diagnosed with generalized lipodystrophy in our registry, while Javor et al. [5] included patients with severe metabolic complications. In addition, the different lifestyle conditions and dietary factors may be modifying disease course and the severity of proteinuria. However, we should note that all patients with CGL older than 26 years were found to have CKD at some level in our registry.

Renal complications were also frequently detected in patients with partial lipodystrophy, although the age of onset was older than those with generalized lipodystrophy. Renal involvement has previously been reported in few patients with FPLD. Owen et al. [20] reported the first case of FPLD who developed mesangiocapillary glomerulonephritis type II

without low circulating C3 levels. Later, several additional patients with FPLD and CKD were reported by different authors [6, 7]. Low levels of circulating C3 have been associated with CKD in patients with APL [3]. Also in our registry, APL was associated with low levels of C3. As shown previously by our group, patients with APL may develop metabolic abnormalities associated with insulin resistance in the course of the disease [21] though it remains unclear if the insulin resistance in our small subset is modified by secondary environmental or genetic factors or primarily due to the underlying lipodystrophy.

A possible explanation for renal involvement may be longstanding poorly controlled diabetes in patients with lipodystrophy. The histopathologic features of diabetic nephropathy in humans are GBM thickening, podocytopenia, mesangial expansion, glomerular and arteriolar hyalinosis, and Kimmelstiel- Wilson nodules [22]. The loss of podocyte function, which contributes to the integrity of the glomerular filtration barrier, is a key event in the development of diabetic nephropathy [23]. Hyperfiltration, which was detected in several patients in our study, is an early abnormality leading to diabetic nephropathy [24]. However, we should note that formula-derived estimations are not always accurate in reflecting real renal function in patients with hyperfiltration or normal kidney functions [19]. Ludtke et al. [8] showed classical findings of diabetic nephropathy such as diffuse and nodular glomerulosclerosis (Kimmelstiel–Wilson lesions) and early ischemic tubulopathy in a post-mortem study. Javor et al. [5] mentioned an autopsy report which revealed diabetic nodular glomerulosclerosis in a patient with CGL. In another postmortem study, Hague et al. [25] described atherosclerotic vascular changes in kidneys. Histopathologically, most patients in our biopsy registry showed several characteristics of diabetic nephropathy such as GBM thickening, mesangial matrix abnormalities, podocyte injury and arterial hyalinosis although there were additional findings remarkable that could not be explained by diabetic nephropathy itself. Also, the lack of diabetic retinopathy in a significant number of patients suggests that additional mechanisms might play a role in the development of CKD in lipodystrophy.

Epidemiological studies have shown that obesity and metabolic syndrome are independent predictors of CKD, which suggests that renal abnormalities may develop long before the appearance of diabetes in patients with insulin resistance [26]. Recently, several researchers described obesity associated proteinuria which progresses to renal dysfunction that was associated with mesangial matrix expansion, glomerular hypertrophy and podocyte injury leading to the development of secondary FSGS. This specific type of FSGS was classified as an adaptive FSGS, which is thought to result from structural and functional adaptations which arise through mechanisms that place hemodynamic stress on an initially normal nephron population [27]. FSGS was a remarkable finding in our biopsy specimens. FSGS has previously been reported in patients with lipodystrophy [4, 5, 28]. One can assume that the pathogenesis of secondary FSGS, which is presumably due to the insulin resistance, might be somewhat common in obesity and lipodystrophy. FSGS may be secondarily mediated by structural-functional adaptations to glomerular hyperfiltration in these patients; however, cell autonomous mechanisms due to underlying genetic abnormalities such as the laminopathy cannot be ruled out. It may be possible that the laminopathy or other genetic defects may predispose the kidney cells to cellular injury and the glomerulosclerosis may be the end-stage progression of cellular damage.

Limited storage capacity of adipose tissue in lipodystrophy results in spillover of dietary and endogenously synthesized triglycerides or other lipids into ectopic sites such as liver which leads to severe insulin resistance [29]. The presence of ectopic lipid vacuoles in the biopsy specimen from our patients provides evidence on ectopic accumulation of triglycerides or other lipids in kidney; however, the potential association of ectopic renal lipid accumulation and renal complications remains unclear. Recent evidence suggests that ectopic renal lipid accumulation may be associated with kidney dysfunction [26, 30]. Studies have demonstrated that ectopic accumulation of lipids in the kidney results in increased expression of sterol regulatory element binding protein (SREBP-1), a key transcription factor in lipogenesis, in obesity prone mice fed a high fat diet. These mice, in turn, developed glomerulosclerosis and proteinuria. Also, transgenic overexpression of SREBP-1 in mice promoted renal injury driven by ectopic lipid accumulation. In contrast, mice lacking SREBP-1 were protected from renal injury when they were challenged on high fat diet [31, 32].

Javor et al. [5] reported a significant decrease in proteinuria and normalization of creatinine clearance in patients with generalized lipodystrophy treated with metreleptin. Ebihara et al. [33] reported a decrease in urinary albumin excretion in 4 Japanese patients with generalized lipodystrophy treated with metreleptin. A significant reduction in the creatinine clearance of 5 patients with glomerular hyperfiltration was also reported in the same study. Later, Chong et al. [34] reported a 51% reduction in 24-hour urinary protein excretion of generalized lipodystrophy patients when they were treated with metreleptin for one year. Very recently, a report from our group described the first patient treated with metreleptin for generalized lipodystrophy in Turkey, which resulted in a significant improvement in glycemic control and lipid profile, and also a significant reduction in urinary protein excretion [35]. While it is reasonable to assume that metreleptin treatment may have a positive impact on the progression of kidney disease in patients with lipodystrophy, the data presented for approval of metreleptin in the US included a number of patients in whom the kidney disease progressed to ESRD while being treated with metreleptin. All of these patients had evidence of reduced GFR at the time of initiation of metreleptin. Therefore, the exact role of metreleptin in the prevention of renal disease associated with lipodystrophy is still not well understood and treatment of patients with reduced GFR should be undertaken with extreme caution and close follow up. The current approval package does state the progression of chronic kidney disease as a potentially possible adverse event of therapy. The impact of the newer treatment strategies on the disease course will have to be evaluated separately, however, recognition of the kidney disease in the natural history of the disease is vitally important not only for the clinicians following these patients but also for both drug developers as well as regulatory agencies.

In conclusion, renal complications are quite common in lipodystrophy syndromes. The kidney involvement is clinically characterized by proteinuria that can progress to nephrotic syndrome and eventually to renal failure. Patients with generalized lipodystrophy are at the highest risk as the onset of renal complications can be early. Renal involvement appears to be multifactorial and may at least be driven by either poorly controlled diabetes and/or the underlying severe insulin resistance. Also, ectopic lipid accumulation or specific genetic mechanisms can potentially play a role; however, further studies are needed to clarify the

specific contributions of each of these factors to the chronic kidney disease of these syndromes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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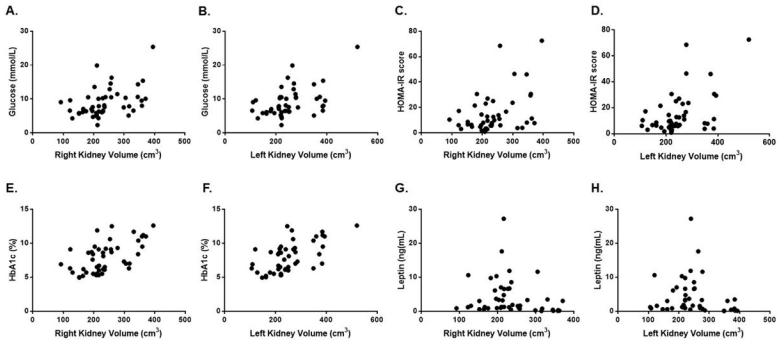

Figure 1.

The association of kidney volume with metabolic parameters (1a–b: Glucose, 1c–d: HOMA-IR score, 1e–f: HbA1c, 1g–h: Leptin).

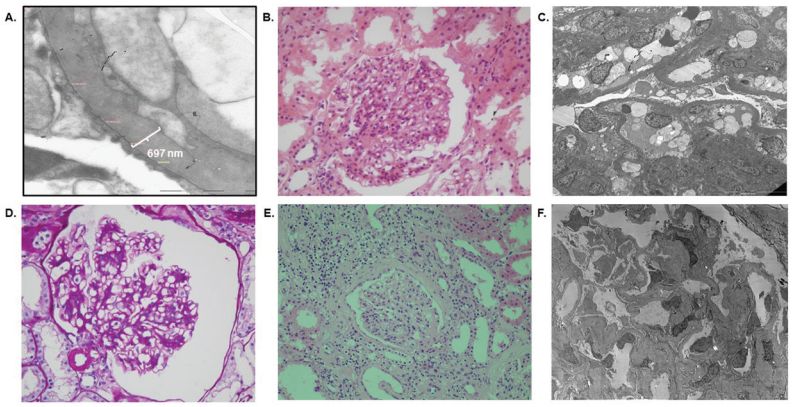

Figure 2.

Renal biopsies performed in patients with lipodystrophy.

Figure 2a: EM image (x6300, patient-1) shows thickening of the GBMs (measured ranging from 587 nm to 1333 nm at different areas).

Figure 2b: LM image (HE x40, patient-1) shows mesangial expansion and hypercellularity. Small arteries and arterioles show hyaline thickening. Small area of FSGS is noted.

Figure 2c: EM image (x500, patient-1) shows podocyte foot process effacement, suggestive of podocyte injury. Lipid vacuoles are visible which suggest ectopic lipid accumulation. No electron dense deposit is detected.

Figure 2d: LM image (PAS x40, patient-1) shows ischemic changes at various levels such as wrinkled GBMs and glomerular shrinkage.

Figure 2e: LM image (HE x20, patient-5) shows mesangial expansion, thickening of GBMs, periglomerular fibrosis, segmental sclerosis, and Kimmelsteil-Wilson nodules.

Figure 2f: EM image (x1000, patient-5) shows widespread areas of podocyte foot process effacement and of collapse.

Clin Endocrinol (Oxf). Author manuscript; available in PMC 2019 July 01.

Table 1

Comparison of metabolic characteristics and renal parameters in patients with generalized lipodystrophy and familial partial lipodystrophy.

	Generalized lipodystrophy (n = 37)	Familial partial lipodystrophy (n = 44)	p value
Age (years)	21 ± 17	38 ± 15	< 0.001
Gender (F/M)	21/16	35/9	0.032
BMI (kg/m^2)	19.05 ± 3.25	23.73 ± 4.87	0.003
Follow-up (months)	72 ± 56	57 ± 84	0.001
Diabetes/ IGT	20 (54%)/ 3 (8%)	31 (71%)/ 4 (9%)	0.221
Duration of diabetes (months)	151 ± 97	127 ± 102	0.403
Hypertension	8 (22%)	17 (39%)	0.147
Glucose (mmol/L)	8.01 ± 4.39	8.18 ± 3.41	0.851
HbA1c (%)	7.63 ± 2.66	7.38 ± 1.94	0.629
HOMA-IR score	19.78 ± 25.21	9.88 ± 9.32	0.025
ALT (IU/L)	56 ± 55	31 ± 24	0.048
GGT (IU/L)	69 ± 72	53 ± 59	0.288
Total cholesterol (mmol/L)	5 ± 2.43	5.66 ± 1.98	0.023
LDL cholesterol (mmol/L)	2.34 ± 1.13	2.94 ± 1.14	0.084
HDL cholesterol (mmol/L)	0.69 ± 0.26	0.89 ± 0.28	0.069
Triglyceride (mmol/L)	7.78 ± 9.42	5.86 ± 5.54	0.258
Leptin (ng/mL)	0.69 ± 0.81	6.47 ± 6.54	< 0.001
Adiponectin (μg/mL)	5.33 ± 7.98	9.01 ± 7.73	0.033
Creatinine (mg/dL)	1.1 ± 1.5	0.67 ± 0.21	0.067
C3 (mg/dL)	137 ± 28	142 ± 24	0.469
CKD	17 (46 %)	23 (52 %)	0.657
eGFR (ml/min/1.73 m^2)	101 ± 48	109 ± 23	0.302
Urinary protein excretion (mg/day)	1061 ± 2982	349 ± 1084	0.15
The median age when CKD was first detected	23 ± 14	41 ±13	0.007
Macroalbuminuria (severely increased albuminuria)	13 (35%)	9 (21%)	0.21
Nephrotic range proteinuria	5 (14 %)	2 (5 %)	0.237

	Generalized lipodystrophy (n = 37)	Familial partial lipodystrophy (n = 44)	p value
eGFR < 60 ml/min/1.73 m^2	8 (22 %)	3 (7 %)	0.1
ESRD, eGFR < 15 ml/min/1.73 m^2	4 (11 %)	None	0.04

ALT: Alanine aminotransferase, BMI: Body mass index, CKD: Chronic kidney disease, C3: Complement-3, eGFR: Estimated glomerular filtration rate, ESRD: end stage renal disease, F: Female, GGT: Gamma-glutamyl transferase, HOMA-IR: Homeostatic model assessment, HDL: High density lipoprotein, IGT: Impaired glucose tolerance, LDL: Low density lipoprotein, M: Male. Data are presented as mean ± standard deviation (SD). Laboratory data shown are collected at the time of final visit.

Clin Endocrinol (Oxf). Author manuscript; available in PMC 2019 July 01.

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Table 2

Clinical features, renal parameters and biopsy results of patients with lipodystrophy.

Patient	Current Age/Gender	Type of lipodystrophy	Clinical features	Age, HbA1c and leptin levels, and renal parameters at the time of biopsy	Biopsy results
1	30/F	CGL homozygous *AGPAT2* c.144C>A (p.C48*)	Diabetes, hypertension, diabetic retinopathy, severe hypertriglyceridemia, recurrent acute pancreatitis episodes, proteinuria, decreased eGFR	Age: 28, HbA1c: 11.2% Leptin: 0.16 ng/ml Urine protein:2.73 g/24 h Serum albumin: 3.5 g/L eGFR: 38 ml/min/1.73 m^2 Serum creatinine: 1.8 mg/dL Serum C3: 128 mg/dL	Mesangial expansion ++ and hypercellularity ++, thickening of GBMs +++, IF/TA +, podocyte foot process effacement +++, arteriolar hyalinosis +++, ischemic changes +++ (wrinkled GBMs and glomerular shrinkage), FSGS (LM/EM), lipid vacuoles (EM), EM and IM negative for any deposit.
2	22/F	CGL homozygous *AGPAT2* c.144C>A (p.C48*)	Diabetes, hypertension, severe hypertriglyceridemia, recurrent acute pancreatitis episodes, nephrotic range proteinuria, hyperfiltration	Age: 21, HbA1c: 10.4% Leptin: 0.1 ng/ml Urine protein:15.2 g/24 h Serum albumin: 3.7 g/L eGFR: 152 ml/min/1.73 m^2 Serum creatinine: 0.37 mg/dL Serum C3: 177 mg/dL	Mesangial expansion ++, thickening of GBMs +, IF/TA +, podocyte foot process effacement ++, arteriolar hyalinosis ++, diffuse mesangial sclerosis, FSGS (LM/EM), EM and IM negative for any deposit.
3	30/F	CGL homozygous *AGPAT2* c.662-2A>C (IVS5-2A>C)	Diabetes, hypertension, diabetic retinopathy, severe hypertriglyceridemia, nephrotic range proteinuria, decreased eGFR	Age: 19, HbA1c: 9.1% Leptin: 0.85 ng/ml Urine protein:10.28 g/24 h Serum albumin: 3.8 g/L eGFR: 20 ml/min/1.73 m^2 Serum creatinine: 3.2 mg/dL Serum C3: 148 mg/dL	Mesangial expansion +, irregular thickening of GBMs +, IF/TA +, arteriolar hyalinosis +++, diffuse mesangial sclerosis, ischemic changes +++ (marked thickening and hyalinization of the vessel walls, narrowing of the vessel lumens, periglomerular fibrosis, wrinkled GBMs and glomerular shrinkage).
4	12/M	AGL	Severe hypertriglyceridemia, recurrent acute pancreatitis episodes, proteinuria, hyperfiltration	Age: 7, HbA1c: 5.4% Leptin: 0.85 ng/ml Urine protein: 2.27 g/24 h Serum albumin: 3.2 g/L eGFR: 154 ml/min/1.73 m^2 Serum creatinine: 0.3 mg/dL Serum C3: 93 mg/dL	Mesangial expansion and hypercellularity +, thickening of GBMs ++, IF/TA +, focal loss of podocyte foot processes, diffuse mesangial sclerosis, small areas of FSGS (LM/EM), lipid vacuoles (EM), EM and IM negative for any deposit.
5	35/F	FPLD heterozygous *LMNA* c.1444C>T (p.R482W)	Diabetes, hypertension, diabetic retinopathy, severe hypertriglyceridemia, nephrotic range proteinuria, decreased eGFR	Age: 35, HbA1c: 11% Leptin: 3.04 ng/ml Urine protein: 3.63 g/24 h Serum albumin: 3.7 g/L eGFR: 57 ml/min/1.73 m^2 Serum creatinine: 1.22 mg/dL Serum C3: 174 mg/dL	Mesangial expansion +++, Kimmelstiel-Wilson nodules, thickening of GBMs +, IF/TA ++, diffuse mesangial sclerosis, arteriolar hyalinosis ++, periglomerular fibrosis, podocyte foot process effacement +, collapsing areas (EM), small areas of FSGS (LM), EM and IM negative for any deposit.
6	24/F	FPLD heterozygous *PPARG* c.452A>G (p.Y151C)	Diabetes, hypertension, severe hypertriglyceridemia, nephrotic range proteinuria	Age: 24, HbA1c: 6.5% Leptin: 8.54 ng/ml Urine protein: 6.28 g/24 h Serum albumin: 3.7 g/L	Mesangial expansion ++ and hypercellularity +, thickening of GBMs +, IF/TA ++, podocyte foot process effacement +, small areas of FSGS (LM),

Patient	Current Age/Gender	Type of lipodystrophy	Clinical features	Age, HbA1c and leptin levels, and renal parameters at the time of biopsy	Biopsy results
				eGFR: 117 ml/min/1.73 m^2 Serum creatinine: 0.72 mg/dL Serum C3: 178 mg/dL	focal collapsing areas (EM), IM positive for IgA deposits.
7	34/F	FPLD Mutation negative	Diabetes, hypertriglyceridemia, proteinuria	Age: 34, HbA1c: 6.7% Leptin: 1.25 ng/ml Urine protein: 491 mg/24 h Serum albumin: 4.1 g/L eGFR: 122 ml/min/1.73 m^2 Serum creatinine: 0.55 mg/dL Serum C3: 126 mg/dL	Irregular thickening of GBMs +, IF/TA +, podocyte foot process effacement ++, arteriolar hyalinosis +, ischemic changes ++ (wrinkling of the GBMs), small areas of FSGS (LM/EM), EM and IM negative for any deposit.
8	50/F	FPLD Mutation negative	Diabetes, hypertriglyceridemia, proteinuria	Age: 50, HbA1c: 9.5% Leptin: 3.35 ng/ml Urine protein:329 mg/24 h Serum albumin: 4.2 g/L eGFR: 103 ml/min/1.73 m^2 Serum creatinine: 0.66 mg/dL Serum C3: 132 mg/dL	IF/TA +, podocyte foot process effacement ++, ischemic changes +++ (marked thickening and hyalinization of the vessel walls, periglomerular fibrosis, wrinkled GBMs and glomerular shrinkage), small areas of FSGS (LM/EM). EM and IM negative for any deposit.
9	33/F	APL	Diabetes, severe hypertriglyceridemia, recurrent pancreatitis episodes, low complement C3 levels	Age: 33, HbA1c: 10.6% Leptin: 1.23 ng/ml Urine protein: 330 mg/24 h Serum albumin: 4.6 g/L eGFR: 129 ml/min/1.73 m^2 Serum creatinine: 0.48 mg/dL Serum C3: 20 mg/dL	Mesangial expansion + and hypercellularity +, thickening of GBMs +, podocyte foot process effacement +, arteriolar hyalinosis +, collapsed glomeruli (EM), lipid vacuoles (EM), EM and IM negative for any deposit.

AGL: Acquired generalized lipodystrophy, *AGPAT2:* 1-acylglycerol-3-phosphate O-acyltransferase 2, APL: Acquired partial lipodystrophy, CGL: Congenital generalized lipodystrophy, C3: Complement-3, eGFR: Estimated glomerular filtration rate, EM: electron microscopy, FPLD: Familial partial lipodystrophy, FSGS: Focal segmental glomerulosclerosis, GBMs: Glomerular basal membranes, IF/TA: Interstitial fibrosis/tubular atrophy, IM: Immunofluorescence microscopy, LM: light microscopy, *LMNA:* Lamin A/C, M: Male, *PPARG:* Peroxisome proliferator-activated receptor gamma.