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Clinical characteristics and efficacy of pioglitazone in a Japanese diabetic patient with an unusual type of familial partial lipodystrophy

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Abstract

This report describes a 46-year-old Japanese diabetic woman with an unusual type of familial partial lipodystrophy. She has marked loss of subcutaneous fat in her lower limbs and buttocks, with sparing of the face, neck, upper limbs, and trunk. This distribution of fat atrophy appears to be rare in comparison with previous reports. Sequencing of candidate genes *LMNA*, *PPARG*, *AKT2*, caveolin-1, as well as the *PPARG4* promoter gene, which are known to be associated with familial partial lipodystrophy, revealed no genetic abnormalities, suggesting that this case may involve a novel gene. Pioglitazone was markedly effective in glycemic control in this case. Her diabetes remained uncontrolled despite a total daily dose of insulin of 30 U and combined treatment with 10 mg of glibenclamide and 0.6 mg of voglibose. We therefore attempted combined treatment with 30 mg of pioglitazone and 30 U/d insulin injection. The hemoglobin A_{1c} level was reduced from 11.2% to 6.1% after 6 months of treatment and has since remained stable. Her body weight increased from 62.0 to 71.0 kg after 12 months of treatment, suggesting that weight gain may result from synergism between thiazolidinediones and insulin-promoting adipogenesis. Pioglitazone increased the fat mass in the upper limbs and trunk, while inducing less increase in the lower limbs, where fat atrophy exists in this patient. Pioglitazone may thus have improved the glycemic control in this case through adipocyte differentiation from progenitor cells mainly in the upper limbs and trunk.

1. Introduction

Understanding of the pathophysiology in lipodystrophy has recently improved [1-4]. Lipodystrophy is a rare disorder characterized by partial or generalized loss of adipose tissue deposits. It is commonly associated with dyslipidemia, hepatic steatosis, and insulin-resistant diabetes. Familial partial lipodystrophy (FPLD) is named after Dunnigan et al [5], who provided a detailed description of the syndrome. In some cases, the lipodystrophy is confined to the limbs, with sparing of the face and trunk, whereas the trunk is also affected with sparing of the face and vulva in other cases. Many cases of FPLD of European origin have been reported to be of the Dunningan et al type, whereas Asian cases of FPLD have only rarely been reported [2,3]. It is thus unclear whether differences in phenotype or genotype of FPLD exist between cases of European origin and of Asian origin. We present here an instructive case of a Japanese diabetic patient with an unusual type of FPLD, with the results of mutational analysis for the *LMNA*, *PPARG*, *AKT2*, and caveolin-1 gene and *PPARG4* promoter gene. We also describe the effectiveness of pioglitazone on glycemic control and the changes of fat and lean mass as measured by dual-energy x-ray absorptiometry (DEXA) scan during pioglitazone treatment.

2. Subject and methods

2.1. Blood samples

Blood was collected after a 12-hour overnight fast for analysis of glucose, insulin, leptin, and adiponectin.

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2.2. Biochemical analyses

Plasma glucose was measured by the glucose oxidase method, and hemoglobin A_{1c} (HbA_{1c}) was measured by a high-performance liquid chromatography method. Serum insulin level was measured using commercial radioimmunoassay kits (Shionogi, Osaka, Japan). Serum leptin level was determined by radioimmunoassay using commercial kits (Linco Research, St Charles, MO). Serum adiponectin level was determined by radioimmunoassay using commercial kits (Otsuka assay, Osaka, Japan) [6].

2.3. Oral glucose tolerance test

A standard oral glucose tolerance test (OGTT) with 75 g of glucose was performed after a 12-hour overnight fast. Venous blood was collected for determination of glucose and insulin concentrations immediately before glucose administration and at 30-minute intervals thereafter for 120 minutes.

2.4. Magnetic resonance imaging technique

Magnetic resonance imaging (MRI) was performed using a 1.5-T imaging device (Sigma Horizon; General Electric, Milwaukee, WI). The upper and lower limbs were surveyed using contiguous axial, 10-mm slices. Fat was easily identified on MRI because of its short T1 relaxation time and its relatively high signal intensity on images compared with other tissues such as muscle.

2.5. Dual-energy x-ray absorptiometry

Whole-body DEXA scan was performed with a multiple detector fan-beam Hologic (Bedford, MA) QDR-4500W densitometer. Data were obtained from the head, upper extremities, trunk, and lower extremities. Proportions of fat in individual regions as well as the whole body were calculated as percentage of body mass. Data were also obtained for measurement of lean tissue mass and bone mineral density.

2.6. Measurement of fat distribution

Subcutaneous and visceral fat distributions were determined by measuring a −150- to −50-Hounsfield unit area using a modification of the method of computed tomographic (CT) scanning (Light Speed Plus-R, General Electric) by Tokunaga et al at the umbilical level [7]. Computed tomographic images were obtained both at baseline and after 9 months of treatment. The V/S ratio was calculated as visceral adipose tissue area divided by subcutaneous adipose tissue area.

2.7. Sequence analyses

Sequence analyses of *LMNA* and *PPARG* were performed in the patient. The patient gave written informed consent for all genetic analyses, which were approved by the Ethical Committee of Kyoto University Graduate School of Medicine. Genomic DNA was isolated from blood using an InstaGene Whole Blood kit (Bio-Rad, Hercules, CA) according to the manufacturer's protocol. Polymerase chain reaction primers, including exon-specific fragments and splice sites, were designed using genomic DNA sequences of human *LMNA* and *PPARG* obtained from GenBank accession numbers NM-170707, AB005520, and AB005526, respectively, as well as published sequences [8,9]. Polymerase chain reaction products were separated by electrophoresis in a 2% agarose gel, purified, and sequenced directly by the chain termination method with both forward and reverse primers on an ABI PRISM310 Genetic Analyzer (PerkinElmer, PE Applied Biosystems, Foster City, CA). All exons and intron-exon boundaries of *AKT2* were amplified and sequenced using primers as previously described [10]. The exons and intron-exon boundaries of caveolin-1 were amplified and bidirectionally sequenced using primers and conditions as previously described [11]. A previously reported method was used to detect the *PPARG4* promoter mutation [12].

3. Case report

The patient is a 46-year-old woman. When she was 34 years old, a diagnosis of diabetes was made by a family physician on the basis of HbA_{1c} and high postprandial glucose levels. However, she decided not to receive any medications for diabetes. She was introduced to our hospital for treatment in December 1998 because of poor glycemic control at 40 years of age. She had a body mass index (BMI) of 23 (height, 160 cm; body weight, 58.5 kg). She had no history of hypertension or autoimmune disease. She was premenopausal status. There was no evidence of axial acanthosis nigricans. In January 1999, HbA_{1c} was 11.6% and her lipid profile was normal (Table 1). An OGTT was performed in September 1999, when she was receiving 10 mg of glibenclamide and 0.6 mg of voglibose and her HbA_{1c} was 8.2%. As shown in Table 2, the insulin levels during OGTT were relatively high, suggesting mild insulin resistance. When serum leptin and adiponectin were measured before her second pioglitazone treatment, she had a BMI of 25.3. Her serum leptin level was 10.4 ng/

Table 1
Biochemical data for this patient

Metabolic variables	Patient
Plasma glucose (mg/dL)	245
HbA_{1c} (%)	11.6
Plasma insulin (μU/mL)	19.1
Serum triglycerides (mg/dL)	137
Serum cholesterol (mg/dL)	200
Serum HDL cholesterol (mg/dL)	49
Serum leptin (ng/mL)	10.4
Serum adiponectin (μg/mL)	3.5

All samples were obtained after a 12-hour overnight fast. HDL indicates high-density lipoprotein.

Table 2
Plasma glucose and insulin levels before and 30, 60, and 120 minutes after an oral 75-g glucose load

	Time (min)			
	0	30	60	120
Plasma glucose (mg/dL)	245	342	409	401
Plasma insulin (μU/mL)	17.7	31.3	79.7	33.0

mL, whereas her serum adiponectin was 3.5 μg/mL (Table 1). An abdominal ultrasound examination revealed hepatic steatosis (unpresented data). She had first noted her decreased subcutaneous fat over her lower limbs at 12 years of age. As shown in Fig. 1B, she exhibited loss of fat in subcutaneous deposits in the lower limbs and buttocks, with prominent lower limbs musculature and excess fat deposition around the face, neck, and trunk. As shown in Fig. 1A, her mother and 2 sisters had a similar physical appearance; and an autosomal dominant pattern of inheritance was therefore considered. A clinical diagnosis of FPLD was therefore made. Her mother had diet-controlled diabetes diagnosed at 75 years of age and died of cerebral infarction at 80 years old. Her father, son, and daughter each had neither fat atrophy nor diabetes mellitus. Her father died of lung cancer at 64 years of age. As shown in Fig. 2, we began initial combined treatment with pioglitazone and insulin injection for diabetes in March 2000, but discontinued pioglitazone in March 2001 because of weight gain. After approximately 3-year washout of pioglitazone, we noted fat atrophy over her lower limbs and assessed body fat distribution by DEXA, MRI, and CT studies in March 2004. As shown in Fig. 1C, T1-weighed MR images at the level of the gluteal fat revealed the striking loss of gluteal subcutaneous fat. As shown in Fig. 1D, axial MRI at the level of the thigh and calf in the patient revealed nearly complete absence of subcutaneous fat in the thigh and calf. As shown in Fig. 1E, axial T1 MRI at the level of the arm and forearm in the patient revealed the preservation of subcutaneous fat. As shown in Fig. 1F, thoracic and abdominal CT revealed preservation of subcutaneous fat in the abdominal and thoracic regions. Table 3 shows the regional and whole-body adipose tissue distribution and body composition estimated by DEXA scan. Compared with healthy subjects, she had markedly decreased fat in her legs, with prominent accumulation in the trunk. Fat accumulation was preserved in her upper limbs. She appeared to have well-preserved skeletal muscle mass.

The first pioglitazone treatment was performed before the diagnosis of FPLD and was markedly effective in improving glycemic control.

Glibenclamide (2.5 mg) and voglibose 0.6 mg/d were started in December 1998; and although the dose of glibenclamide was increased to 10 mg/d, her HbA_{1c} was 9.5% and remained high. Injection of biphasic human insulin (BHI 30) was added at a dose of 16 U/d, and the dose of insulin was increased to 30 U/d; but HbA_{1c} was still 8.0%, and her blood glucose level remained unsatisfactory. Her body weight gain was about 3 kg, and BMI was increased to 24.4 during combined treatment with glibenclamide and insulin. We stopped the glibenclamide and prescribed metformin 500 mg/d, but HbA_{1c} increased to 11.2%. We therefore discontinued the metformin and initiated combined treatment with pioglitazone (30 mg/d) and insulin in March 2000. Her response to pioglitazone was monitored by HbA_{1c}. Fig. 2 shows HbA_{1c} level during treatment. Decline in HbA_{1c} was observed at 2 months; and the decrease continued to be observed throughout the treatment, with lowest values at 6 months. After 6 months of treatment, HbA_{1c} had decreased from 11.2% to 6.1% and remained thereafter at about 6.0%. After 7 months of treatment, the dose of insulin was decreased to 20 U/d. Fig. 2 also shows change in body weight during treatment. After 12 months, body weight had increased from 62.0 to 71.0 kg. We stopped pioglitazone in March 2001 because of this weight gain.

3.1. Changes in body fat distribution and serum adiponectin during the second pioglitazone treatment

About 3 years had passed since she received the combined treatment with 4 mg glimepiride and 30 U/d insulin injection (BHI 30) instead of pioglitazone. Her blood glucose level remained unsatisfactory. We therefore began administration of a half-dose (15 mg) of pioglitazone in April 2004 to prevent body weight gain. Change in fat and lean mass was monitored during pioglitazone treatment by DEXA scan. We also evaluated changes in subcutaneous and visceral fat area by abdominal CT and adiponectin level during pioglitazone treatment. After 9 months of treatment, HbA_{1c} level was reduced from 8.5% to 6.2% and remained stable thereafter, whereas body weight increased by about 3 kg (Fig. 3). As shown in Table 4, comparison of DEXA scan results showed that fat mass increased by 2.2 kg, whereas lean mass increased by 0.7 kg during pioglitazone treatment. Pioglitazone induced increase in fat mass almost equally in the upper limbs, lower limbs, and trunk, although the increase was slightly less in the lower limbs than in the other 2 regions. Interestingly, the increase in lean mass in the lower limbs was greater than that in the upper limbs and trunk, whereas the increase in lean mass in the upper limbs and trunk was suppressed. We also evaluated the accumulation of subcutaneous and visceral fat by CT scan at the umbilical levels before and after 9 months of pioglitazone treatment. Pioglitazone increased subcutaneous fat from 160.0 to 211.3 cm^2, but resulted in almost no change in visceral fat (103.7 vs 106.2 cm^2). After 9 months of treatment, serum adiponectin had increased from 3.5 to 21.7 μg/mL.

3.2. Sequence analysis

We examined the sequences of the entire coding regions and exon-intron boundary regions of the *LMNA*, *PPARG*,

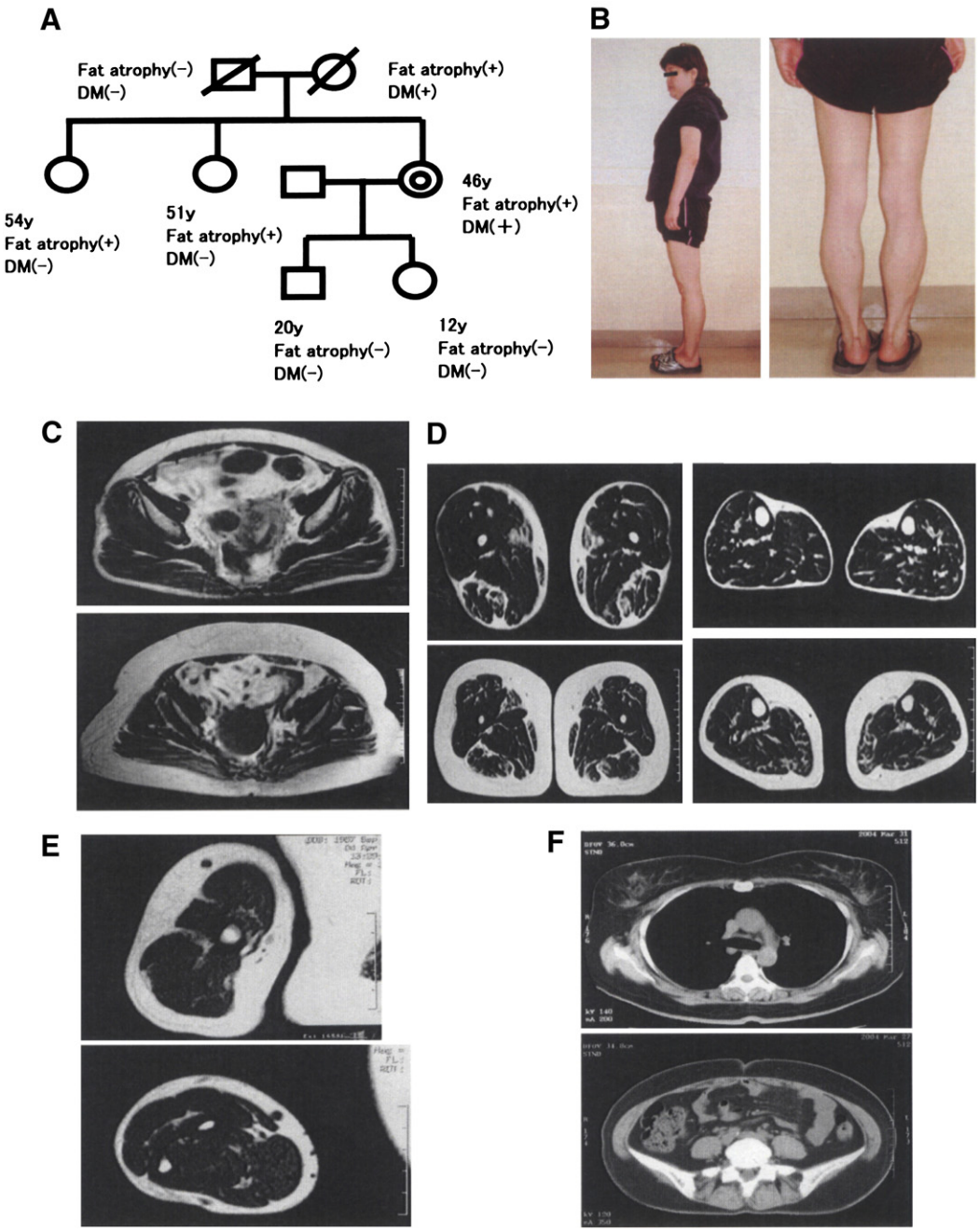

Fig. 1. A, The pedigree of a Japanese family with an unusual type of FPLD. The proband, her mother, and 2 sisters exhibited marked loss of subcutaneous fat in the lower limbs and buttocks. The proband and her mother had diabetes mellitus. B, Phenotypic features of the patient. Note the prominent lower limbs musculature as well as the preservation of abdominal and cervical fat with loss of lower limbs and gluteal fat deposits. C, T1-weighted MR images at the level of the gluteal fat indicate striking loss of gluteal subcutaneous fat in the upper panel. Control images obtained from a healthy female individual are shown in lower panel. D, T1-weighted MR images at the level of the thigh (left panel) and calf (right panel) in the patient reveal nearly complete absence of subcutaneous fat. Control images obtained from a healthy female individual are shown in the lower panel. E, T1-weighted MR images at the level of the arm (upper panel) and forearm (lower panel) in the patient indicate preservation of subcutaneous fat. F, Thoracic CT at the level of the fourth thoracic vertebrae and abdominal CT at the umbilical level. Thoracic (upper panel) and abdominal (lower panel) findings reveal that CT showed the preservation of subcutaneous fat in the abdomen and thoracic region.

AKT2, and caveolin-1 genes, but found no mutations of these genes in the proband. We also checked for −14A>G substitution upstream from exon 1 within the *PPARG4* promoter, but did not find this mutation.

4. Discussion

In this article, we have described a 46-year-old Japanese diabetic woman with an unusual type of FPLD. She has

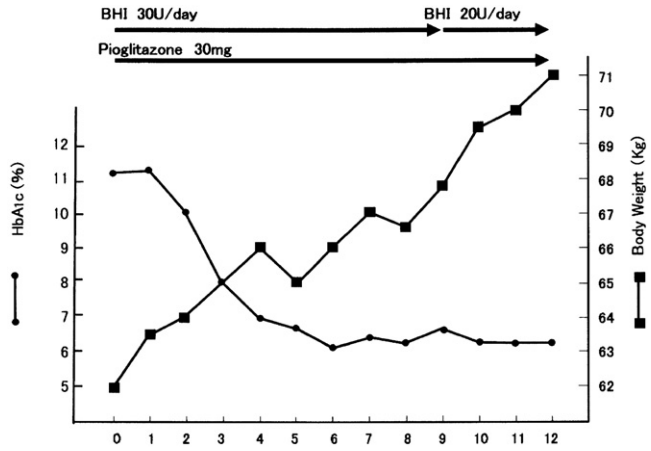

Fig. 2. Hemoglobin A_{1c} level and body weight during the first pioglitazone treatment. Pioglitazone (30 mg) was administered and dramatically improved glycemic control. However, it was stopped because of body weight gain.

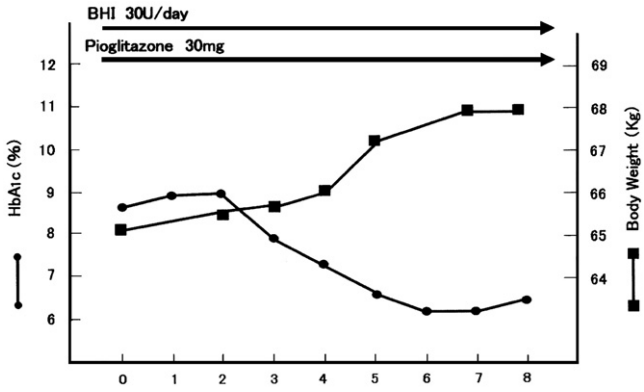

Fig. 3. Hemoglobin A_{1c} level and body weight during the second pioglitazone treatment. The dose of pioglitazone was 15 mg to prevent excessive body weight gain. Changes in body fat composition were evaluated by DEXA scan and abdominal CT as well as serum adiponectin level after 9 months of pioglitazone treatment.

marked loss of subcutaneous fat in her lower limbs and buttocks, with sparing of the face, neck, upper limbs, and trunk. The cases of FPLD reported thus far have predominantly affected the limbs and gluteal fat deposits, with variable truncal involvement but normal or excess fat on the face and neck [2,5,13-16,18-20]. The distribution of fat atrophy in the present case thus appears to be rare.

The loss of body fat in FPLD can be caused by defects in the development and/or differentiation of adipose tissue as a consequence of mutations in a number of genes, including *LMNA*, *PPARG*, *AKT2*, and caveolin-1 [2,15]. Patients with *LMNA* gene mutation have FPLD as indicated by a loss in subcutaneous fat in the upper and lower limbs [2,17]. Patients with *PPARG* gene mutation also have FPLD, as indicated by a loss of fat in subcutaneous deposits in the limbs, affecting the distal regions of the extremities such as the forearms and calves more than the proximal regions, but with preservation of visceral and abdominal subcutaneous fat [2,18-20]. It appears likely that our patient has no mutation of the *LMNA* or *PPARG* gene because she has a phenotype of lipodystrophy distinct from that of patients with *LMNA* gene or *PPARG* gene mutation.

Recently, George et al [10] reported a heterozygous missense mutation R274H in the *AKT2* gene in a family in which affected subjects developed insulin resistance, diabetes mellitus, and hypertension. The proband, a 34-year-old woman, had partial lipodystrophy affecting her extremities. Cao et al [15] also reported a heterozygous

Table 3
Body composition as determined by DEXA scan in the proband

	Proband	Mean values (in control subjects)
Height (cm)	160.0	156.1 ± 4.9
Body weight (kg)	64.0	55.1 ± 6.7
BMI (kg/m^2)	25.0	22.7 ± 3.0
Age (y)	46	45.1 ± 2.8
Fat (%)		
Whole body	33.1	30.3 ± 6.2
1 Arm	42.9	26.9 ± 7.3
1 Leg	13.0	33.2 ± 5.7
Trunk	40.4	28.4 ± 7.7
Fat mass (kg)		
Whole body	20.2	16.8 ± 5.2
1 Arm	1.3	0.7 ± 0.3
1 Leg	0.9	3.5 ± 1.0
Trunk	15.0	7.1 ± 2.8
Lean mass (kg)		
Whole body	38.8	35.3 ± 3.1
1 Arm	1.7	1.7 ± 0.2
1 Leg	5.4	6.6 ± 0.9
Trunk	21.5	16.3 ± 1.3

Normal values are obtained from 55 healthy middle-aged women. Fat, fat mass, and lean mass in 1 arm and leg indicate the mean values of left and right arm (or leg).

Table 4
Changes in fat and lean mass determined by DEXA, subcutaneous and visceral fat areas determined by abdominal CT, and serum adiponectin level during pioglitazone treatment

	Pioglitazone		
	Pre	Post	Change
Body weight (kg)	65.0	68.0	+3.0
Fat (kg)			
Whole body	20.2	22.4	+2.2
Arms	2.7	3.5	+0.8
Legs	1.7	2.2	+0.5
Trunk	15.0	15.9	+0.9
Lean mass (kg)			
Whole body	38.8	39.5	+0.7
Arms	3.3	3.1	−0.2
Legs	10.8	11.9	+1.1
Trunk	21.5	21.3	−0.2
CT (umbilical level)			
Subcutaneous fat (cm^2)	160	211.3	+51.3
Visceral (cm^2)	103.7	106.2	+2.5
Adiponectin (μg/mL)	3.5	21.7	+18.2

caveolin-1 frameshift mutation in patients with atypical partial lipodystrophy and hypertriglyceridemia. We were therefore interested in the possibility of involvement of the *AKT2* and caveolin-1 genes in this case and added mutational analysis, including *AKT2* and caveolin-1. However, we found no mutations in these genes. This case thus features an unusual phenotype, with no mutation of the causing gene in FPLD, *LMNA*, *PPARG*, *AKT2*, caveolin-1, and *PPARG4* promoter. It is thus possible that the present case is due to a defect of a novel gene. However, we could not analyze messenger RNA (mRNA) of candidate gene in this article; and we could not rule out the following possibility. The mutation might be located anywhere except the entire coding regions and exon-intron boundary regions in candidate gene. It might either cause the dysfunction of mRNA of candidate gene or, alternatively, decrease levels of mRNA of candidate gene [21].

Pioglitazone was markedly effective in improving glycemic control in our case. As shown in Fig. 2, HbA_{1c} level decreased by 5.1% in our patient after 6 months of treatment with pioglitazone. Marked weight gain was also observed in our patient during pioglitazone treatment. This observation was compatible with a previous report [14], suggesting that it may result from synergism between thiazolidinediones (TZDs) and insulin-promoting adipogenesis. The level of adiponectin was low before treatment, but increased markedly during pioglitazone treatment. Thiazolidinediones seemed ideally suited to treat lipoatrophic diabetes [22]. Almost all diabetic patients in this study had partial lipodystrophy. In the 13 patients with diabetes who completed 6 months of troglitazone treatment, HbA_{1c} levels significantly decreased by a mean of 2.8%.Troglitazone treatment significantly increased body fat without significant change in weight. Savage et al [18] reported that subject 2 (S2) with FPLD was heterozygous for a proline-467-leucine (P467L) mutation in *PPARG*, whereas subject 3 (S3) with FPLD was heterozygous for a valine-290-methionine (V290M) mutation in *PPARG*. The metabolic impact of rosiglitazone was much more striking in S2, in whom insulin sensitivity and HbA_{1c} were both normalized, whereas S3 remained severely insulin resistant and exhibited little change in HbA_{1c}. Fat mass was increased by 3.5 kg in S2 and was increased by 4.0 kg in S3 after rosiglitazone treatment for 6 months, indicating that rosiglitazone induced adipocyte differentiation in both cases. Adiponectin level was low before treatment and showed slight increase in both cases. Owen et al [23] also reported no clear advantages in treating patients with FPLD caused by a mutation in the *LMNA* gene (R482W) with rosiglitazone despite increases in subcutaneous adipose tissue. The effects of TZDs on glycemic control, body weight, and adiponectin thus appear to vary in patients with various forms of FPLD [14,18,22-24].

We also measured changes in fat and lean mass during pioglitazone treatment by DEXA scan. As shown in Table 4, fat mass increased by 2.2kg, whereas lean mass increased by 0.7 kg during pioglitazone treatment. Table 4 also shows that subcutaneous fat in the abdomen increased during pioglitazone treatment, consistent with a previous report [7]. Pioglitazone induced increase in fat mass almost equally in the upper limbs, lower limbs, and trunk, although the increase was less in the lower limbs than in the other 2 regions, suggesting a defect in adipocyte differentiation in the lower limbs where fat atrophy exists. Pioglitazone may thus improve glycemic control through adipocyte differentiation from progenitor cells mainly in the upper limbs and trunk [25,26].

Garg [27] has reported that women with Dunnigan-type FPLD have twice the prevalence of diabetes and more than 3 times the prevalence of atherosclerotic vascular disease as men. The mother of our patient with partial lipodystrophy had diabetes and died of cerebral infarction. Regular evaluation for atherosclerosis will therefore be required in this patient.

In conclusion, we have described the phenotype of a case of FPLD case of Asian origin, which differs from that of FPLD cases of European origin. As there were no mutations in the causative genes of *LMNA*, *PPARG*, *AKT2*, caveolin-1, and *PPARG4* promoter, known to be associated with FPLD, it may be that a novel gene is involved in this case. More FPLD cases of Asian origin will need to be examined to determine the clinical features, phenotype, and genotype of Asian cases of FPLD.

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