Efficacy of pioglitazone in familial partial lipodystrophy of the Dunnigan type: a case report


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Abstract

A 25 year old woman consulted for a severe acanthosis nigricans and central distribution of fat. Her masculine type morphology was associated with muscular appearance of the limbs and excess fat deposits in the face and neck. Biological testing confirmed glucose intolerance associated with a severe insulin resistance, hypertriglyceridemia and polycystic ovary syndrome. The detection of a heterozygous missense mutation in LAMIN A/C gene at position 482 confirmed the diagnosis of Familial Partial Lipodystrophy (FPLD2). Due to a deterioration of clinical and metabolic status, 15 and then 30 mg per day of pioglitazone were added to her previous treatment with metformin, bezafibrate and omega-3 fatty acids. Metabolic status improved rapidly after 3 months and continued thereafter. Weight remained stable, body mass composition and waist circumference improved. After 18 months of treatment, glycaemia and triglycerides levels normalized, hepatic enzymes and liver echographic features improved. Insulin sensitivity improved dramatically with a HOMA % S value of 73% with metformin and of 98.2% when pioglitazone was added. Leptin levels increased from 6.6 to 10.2 μg/ml. We report a very rapid and good efficacy of pioglitazone added to metformin without side effects in FPLD2. If confirmed on more patients, early use of pioglitazone in association with metformin could be proposed in FPLD2.

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Résumé

Efficacité de la pioglitazone dans la lipodystrophie familiale partiel de Dunnigan : à propos d’un cas

Une femme de 25 ans consulte pour une acanthosis nigricans sévère et une obésité centrale. Cette morphologie masculine est associée à une très forte musculature des membres inférieurs et des dépôts de tissu adipeux au niveau du visage et du cou. Les examens biologiques confirment la présence d’une insulinorésistance sévère compliquée d’une intolérance au glucose, d’une hypertriglycéridémie et d’un syndrome des ovaires polykystiques. La découverte d’une mutation faux-sens à l’état hétérozygote du gène de la LAMINE A/C en position 482 confirme le diagnostic de lipodystrophie partiel familiale de Dunnigan (FPLD2). Du fait d’une détérioration de l’état clinique et métabolique sous metformine, bézafibrate et acides gras oméga 3, des doses de 15 puis 30 mg de pioglitazone sont ajoutées. L’amélioration métabolique apparaît dès le troisième mois se poursuit au cours des 18 mois de suivi. Le poids reste stable, la composition corporelle et le tour de taille s’améliorent. La glycémie et les triglycérides sont normalisés, les résultats des enzymes hépatiques et de l’échographie hépatique sont améliorés. La sensibilité à l’insuline aug-

Abbreviations: FPLD2, Dunnigan-type-familial partial lipodystrophy; BMI, Body mass index; OGTT, Oral glucose tolerance test; PPARy, Peroxisome proliferator activated receptor y.

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1. Introduction

Dunnigan type familial partial lipodystrophy (FPLD2) is a rare autosomal dominant disorder clinically characterized by the gradual appearance at puberty of peripheral fat loss, excess accumulation of fat around the neck and chin, perivisceral adiposity and muscular hypertrophy predominant in the lower limbs. Approximately one third of affected women develop adiposity and muscular hypertrophy predominant in the lower limbs. The severity of FPLD2 is due to its association with metabolic alterations: insulin resistance, diabetes, hypertriglyceridemia that can lead to acute pancreatitis and hepatic steatosis, reduced HDL – cholesterol and adiponectin [3]. Premature atherosclerosis, in particular early ischemic disease is a major risk [4, 5].

The prevalence of FPLD2 is about 1 in 200 000 [4]. Despite the autosomal dominant transmission of the disease, FPLD2 is more severe in women than in men, both at clinical and biological levels [6]. FPLD2 belongs to the group of diseases linked to LMNA mutations called laminopathies [2]; they comprise at least eight different conditions, from muscular dystrophies to lipodystrophies and premature ageing syndromes [7]. The LMNA gene encodes type-A lamins, which are nuclear proteins with both structural and regulatory roles in differentiated cells. Heterozygous mutations cause typical FPLD2 cluster in exons 8 and 11 of LMNA, encoding the globular C-terminal domain of type A-lamins that interacts with several partners, including DNA. The most frequent FPLD2 – linked LMNA mutation, present in about 85% of patients substitutes a basic amino-acid at position 482 (arginine) for a neutral one (tryptophane, glutamine, leucine).

Very few studies have evaluated FPLD2 therapy. Although insulin resistance is a key feature in FPLD2, treatment with the insulin sensitizers glibizamide has only been reported in three articles concerning either troglitazone [8] or rosiglitazone [9, 10]. In addition, the 2 FPLD2 patients treated with rosiglitazone showed different responses to treatment. Owen [9] reported no improvement in glycaemic control and even a worsening in lipid profile; while Lüdtke [10] showed an improvement in glycaemic control and dyslipidemia but progressive myalgia associated with chest and abdominal pain lead to a reduction of the dose of rosiglitazone. Neither significant cardiac nor hepatic side - effects were observed in these studies.

We now report a rapid and sustained response to pioglitazone, on metabolic parameters and body composition in a woman with FPLD2.

2. Case report

A 25 year old patient consulted for acanthosis nigricans on the neck and axilla associated with central obesity. At presentation, she had a masculine type of morphology with a Body Mass Index (BMI) of 26.7 kg/m², a weight of 79 kg for a height of 172 cm and a waist circumference of 99 cm. She showed a muscular hypertrophy of the limbs and shoulders, without any functional muscular abnormalities, and a severe lipoatrophy, predominantly in legs and forearms. Blood pressure (BP) was 145/85 mmHg. Pubertal development had been normal with spontaneous menstruations at age 13. She complained of menstrual irregularities since puberty associated with mild hirsutism. She was previously diagnosed with polycystic ovaries.

The diagnosis of polycystic ovary syndrome was established for acanthosis nigricans on the neck and axilla associated with central obesity. At presentation, she had a masculine type of morphology with a Body Mass Index (BMI) of 26.7 kg/m², a weight of 79 kg for a height of 172 cm and a waist circumference of 99 cm. She showed a muscular hypertrophy of the limbs and shoulders, without any functional muscular abnormalities, and a severe lipoatrophy, predominantly in legs and forearms. Blood pressure (BP) was 145/85 mmHg. Pubertal development had been normal with spontaneous menstruations at age 13. She complained of menstrual irregularities since puberty associated with mild hirsutism. She was previously diagnosed with polycystic ovaries.

The oral glucose tolerance test (OGTT) showed glucose intolerance with severe insulin resistance (Table 1). Triglycerides levels were 5.4 mmol/l (N < 1.71). Serum liver enzymes being elevated in the absence of any obvious cause of liver cytolyis; a CT scan was performed and showed hepatic steatosis. Free testosterone levels were 15.3 pg/ml (N < 12.5); delta 4 androstenedione was 3.7 ng/ml (N < 3.1), LH increased from 9.3 to 110 mU/ml and FSH from 3 to 8 mU/ml. A 21 hydroxylase deficiency was ruled out by a normal 17OH progesterone response to the ACTH test. Polycystic ovaries were observed upon ovarian ultrasound examination. The diagnosis of polycystic ovary syndrome was established and cyproterone – acetate associated with 17 β estradiol was prescribed.

The mother and maternal uncle had a comparable but lighter phenotype; none of them had diabetes. The uncle had hypertriglyceridemia. Maternal fertility and menstrual cycles had been normal.

Sequencing of the LMNA gene from the proband, performed as previously described [6], established the diagnosis of FPLD2; we identified a heterozygous missense mutation at position 482, located in exon 8 in LMNA that predicted an arginine to glutamine substitution. The mother and maternal uncle were tested and the same mutation identified.

At age 35, the proband had a BMI of 28.6 kg/m², blood pressure of 120/80 mmHg with 20 mg of betaxolol qd. Metabolic status deteriorated progressively (Table 2) despite the administration of metformin 1000 mg twice daily (maximal dose tolerated), bezafibrate (200 mg qd) and omega-3 fatty acid.
acids 6g per day. Nodular hepatic steatosis was diagnosed upon MRI examination.

Pioglitazone 15 mg per day was added to previous treatment during one month, and after checking for hepatic tolerance, dose was increased to 30 mg per day. Clinical and metabolic improvement occurred within 3 months. At that time, waist circumference was 92 cm, glycaemia was 5.1 mmol/l, and triglycerides were 1.6 mmol/l. After 6 months, body weight and total body fat mass remained stable with unmodified food intake and diabetic hypo caloric diet. A little amount of subcutaneous fat appeared around the hips but not in the arms and legs and leptin increased under pioglitazone. Biological parameters normalized except for HDL cholesterol (Table 2). After 18 months of therapy, acanthosis nigricans had disappeared and glucose tolerance and insulin sensitivity improved dramatically (Table 1). The abdominal ultrasound examination showed the disappearance of the nodular liver steatosis. No side effects due to pioglitazone were reported.

3. Discussion

Cardiovascular disease, diabetes and acute pancreatitis are the main complications of FPLD. In addition, skeletal or cardiac muscular alterations specific to other laminopathies may also be associated with FPLD2 [11]. However to our knowledge, junctional tachycardia has never been reported in patients with FPLD2. Complete cardiac testing in our patient eliminated any cardiac failure or cardiomyocardiopathy allowing us to prescribe pioglitazone.

Our patient had also Scheuermann’s disease that was probably coincidental, given the high prevalence of this condition; however it is noticeable that bony alterations have been described in other laminopathies with lipodystrophy such as mandibulo-acral dysplasia.

Improving cardiovascular disease and triglyceridemia is mandatory in FPLD2 [12]. In our patient, addition of pioglitazone to metformin, bezafibrate and omega-3 fatty acids, lead to specific positive effects on glucose control and triglyceride levels as previously reported by Arioglu in FLDP patients [8] using troglitazone and by Lüdtke, but not by Owen using rosiglitazone [9,10]. Pioglitazone was chosen for the known higher effectiveness of this molecule on triglyceride levels compared to rosiglitazone [13]. Indeed, we obtained for the first time a normalization of triglyceride levels in this patient after 3 months of treatment. In addition, HDL levels remained unchanged over time. LDL levels tended to decrease while they increased in the observation reported by Owen. Therefore, as compared to rosiglitazone, pioglitazone could be more appropriate to improve FPLD2 lipids abnormalities.

While Owen described a 5 kg weight increase under rosiglitazone in a FPLD patient, weight remained stable in our patient; this may be explained by the use of the association of metformin to pioglitazone which has been shown to limit

Table 1
Evolution of OGTT: glycaemia, insulin levels and HOMA values, at baseline, with metformin alone and with metformin and pioglitazone

<table>
<thead>
<tr>
<th>Glycaemia (mmol/l) (N:3.9–6.1)</th>
<th>Insulin (mUI/l) (N:2–15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At presentation</td>
<td>With metformin alone</td>
</tr>
<tr>
<td><strong>T0</strong></td>
<td>5.4</td>
</tr>
<tr>
<td><strong>T15</strong></td>
<td>9.4</td>
</tr>
<tr>
<td><strong>T30</strong></td>
<td>11.9</td>
</tr>
<tr>
<td><strong>T45</strong></td>
<td>11.9</td>
</tr>
<tr>
<td><strong>T60</strong></td>
<td>11.6</td>
</tr>
<tr>
<td><strong>T90</strong></td>
<td>9.8</td>
</tr>
<tr>
<td><strong>T120</strong></td>
<td>8.3</td>
</tr>
<tr>
<td><strong>T180</strong></td>
<td>7.9</td>
</tr>
</tbody>
</table>

Table 2
Evolution of clinical and biological parameters after pioglitazone introduction

<table>
<thead>
<tr>
<th>Clinical and biological parameters</th>
<th>With metformin before pioglitazone</th>
<th>After 6 months of pioglitazone and metformin</th>
<th>After 18 months of pioglitazone and metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>84.5</td>
<td>83.0</td>
<td>83.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6</td>
<td>28.1</td>
<td>28.1</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>99.0</td>
<td>92.0</td>
<td>93.0</td>
</tr>
<tr>
<td>Impedancemetry (% total fat mass)</td>
<td>39.5</td>
<td>38.0</td>
<td>38.5</td>
</tr>
<tr>
<td>Glycaemia (mmol/l) (N: 3.9–6.1)</td>
<td>5.6</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>HbA₁c (% (N &lt; 6)</td>
<td>6.2</td>
<td>5.7</td>
<td>5.7</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l) (N &gt; 1.16)</td>
<td>0.98</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l) (N &lt; 3.87)</td>
<td>2.5</td>
<td>2.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Triglyceridemia (mmol/l) (N: 0.57–1.71)</td>
<td>3.0</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Leptin (μg/ml) (N: 3.17–11)</td>
<td>6.6</td>
<td>10.1</td>
<td>10.4</td>
</tr>
<tr>
<td>SGPT (UI/l) (N &lt; 36)</td>
<td>54.0</td>
<td>41.0</td>
<td>32.0</td>
</tr>
</tbody>
</table>
the weight gain due to glitazones in type 2 diabetic patients [14]. Interestingly, waist circumference decreased significantly in our observation, confirming Arioglu’s results with troglitazone [8] showing a decrease in visceral abdominal fat with treatment. Visceral adipose tissue is known to be a major contributor to insulin resistance and a modification in abdominal fat has been reported with the use of glitazones in type 2 patients [15]. In our patient, amount of total body fat mass evaluated by impedancemetry was not significantly modified during treatment but a small amount of subcutaneous fat appeared around the hips. In addition, as in Owen’s report, the patient’s leptin levels increased with glitazone administration.

Indeed, subcutaneous adipose tissue secretes three times as much leptin as the omental adipose tissue [16]. All together, these modifications are in favour of a fat redistribution from the abdomen to the subcutaneous localisation, which is a recognised action of glitazones [15].

The triglyceride storage capacity can be increased by PPARγ (peroxisome proliferator activated receptor γ) agonists, which are known inducers of adipocytes differentiation. The metabolic improvement observed with glitazones could thus be due, at least partially, to an increase in both triglycerides storage capacity and leptin secretion by newly differentiated subcutaneous adipocytes [17]. As expected, our patient significantly improved her insulin sensitivity evaluated using HOMA %S [18]. The OGTT at 18 months of treatment showed a dramatic decrease in insulinemia and glycemia at T 180, as compared with the OGTT performed under metformin, bezafibrate and omega-3 fatty acids before introducing pioglitazone. Acanthosis nigricans of the neck and axillary regions disappeared, clinically confirming the insulin sensitivity improvement. This may be explained by the synergy of the insulin sensitizing mechanisms of metformin and glitazone with their distinct effects on hepatic and peripheral glucose homeostasis.

The HOMA %B improvement may be due to decrease in glucose toxicity and perhaps a specific effect of glitazones since they have been involved in beta cells protection in animal studies [15].

Pioglitazone has been shown to be an effective therapy of Non Alcoholic Steato - Hepatitis (NASH); in a pilot study on 18 non diabetic patients, 72% of patients had a normalization of liver enzymes and 2/3 had a significant improvement of histologic score for steatosis, cellular injury, parenchymal inflammation and fibrosis after 48 weeks of treatment [19,20]. Liver steatosis is part of the phenotype in FLDP [21] and the improvement of liver enzymes and imaging under pioglitazone in our patient further suggests that pioglitazone, by increasing insulin sensitivity, is able to improve liver steatosis even in this syndrome of severe insulin resistance.

The molecular abnormalities described in FPLD2 could explain the good response to PPARγ agonists. The precise pathophysiology of FPLD2 is currently still unknown, but it could involve an altered interaction between mutated type A lamins and the adipogenic transcription factor SREBP-1 (sterol – regulatory element – binding protein 1) thus impairing the adipose differentiation program [22]. PPARγ agonists, by allowing a bypass of SREBP-1 during the adipocyte differentiation process, could rescue this alteration, as suggested by recent in vitro studies [23].

Compared to the previous reports, we suggest here a very good efficacy of the pioglitazone compared to the results reported in the case reports concerning rosiglitazone in FPLD2. The weight gain was lower and the insulin sensitivity as well as lipid profile improvement greater than previously described with the use of rosiglitazone. This may be due to the synergy between metformin and pioglitazone [14]; these drugs being used in combination in our patient, and to pioglitazone specific actions on lipid metabolism. If confirmed on more patients, a very early use of pioglitazone combined with metformin could be proposed in FPLD2. Glitazones are eventually protective against beta – cell apoptosis and cardiovascular risk.

Acknowledgments

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