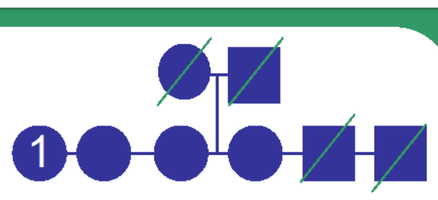
Familial partial lipodystrophy type 3 due to PPAR-gamma mutation: presentation with diabetes and severe hypertriglyceridemia

Joana Oliveira[1,3,4], Filipe Cunha[1,3,4], Elisabete Rodrigues[1,3,4], Joana Menezes Nunes[1,3,4], Ana Saavedra[1,3,4], Maria Manuel Costa[1,3,4], Daniela Magalhães[1,3,4], Rita Bettencourt-Silva[1,3,4], Susana Fernandes[2,3], João Paulo Oliveira[2,3], Davide Carvalho[1,3,4], Paula Freitas[1,3,4]

[1]Endocrinology, Diabetes and Metabolism Department, Centro Hospitalar São João; [2]Department of Genetics, Centro Hospitalar São João; [3]Faculty of Medicine, University of Porto; [4]Institute for Innovation and Health Research, University of Porto - Porto, Portugal

Introduction: Familial partial lipodystrophy (FPL) is an autosomal dominant disease characterized by selective loss of subcutaneous fat from the extremities and gluteal region, with lipohypertrophy of the face, neck and trunk. It is usually tightly linked with severe metabolic complications. FPL type 3 results from peroxisome proliferator-activated receptor gamma (PPAR-gamma) mutations.

1 53-year-old Caucasian woman



ENDOCRINOLOGY DEPARTMENT (04/10/2013)

Severe dyslipidemia - hypercholesterolemia and hypertriglyceridemia (11729 mg/dL)

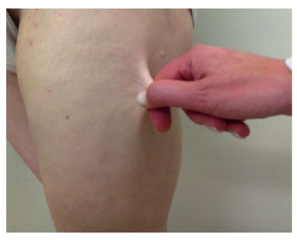
"Type 2" diabetes

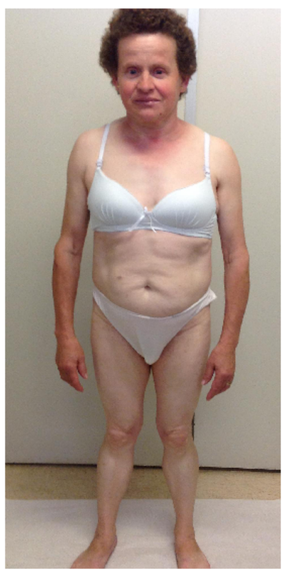
Diabetes mellitus since she was 37 years old
*Diabetic nephropathy
Arterial hypertension
Nontoxic multinodular goiter
No history of pancreatitis or cardiovascular disease

Medication
Insulin detemir 52 units at breakfast + 52 units at bedtime
Insulin lispro: 8 units at breakfast + 8 units at lunch + 8 units at dinner
Vildagliptin/metformin 50/1000 mg twice daily
Simvastatin 20 mg once daily
Fenofibrate 267 mg once daily
Aspirin 100 mg once daily
Enalapril 20 mg once daily

POOR THERAPEUTIC COMPLIANCE

Medical family history
Mother died at 55 years old from stroke (she had diabetes and dyslipidemia)
Father died at 65 years old from lung cancer
1 brother died at 31 years old from acute myocardial infarction
1 sister was diagnosed with a meningioma; 2 sisters had diabetes, arterial hypertension and dyslipidemia



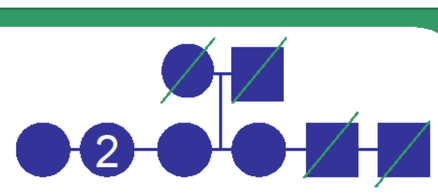


Physical Examination
Weight: 50.3 kg | Height: 1.47 m | BMI: 23.3 kg/m²
Waist circumference: 80 cm
BP 152/81mmHg, HR 97bpm
No xanthomas, xanthelasmas or lipemia retinalis
Lipoatrophy of the extremities with preserved subcutaneous fat in face and trunk

Laboratory tests
A1c **10.3%**
Total cholesterol **921** mg/dL; HDL cholesterol **56** mg/dL; LDL cholestrol **195** mg/dL; triglycerides **4679** mg/dL; apolipoprotein B 99 mg/dL (53-138); lipoprotein(a) 4.3 mg/dL (<30)
AST **34** U/L (10-31); ALT < 3 U/L (10-31); GGT **40** U/L (7-32); ALP 63 U/L (30-120)
Creatinine 0.49 mg/dL (0.51-0.95)
Urine albumin-to-creatinine ratio **108.4** mg/g
TSH 2.09µUI/mL (0.35-4,94); T4L 1.00ng/dL (0.70-1.48)
Lipemic serum, with milky appearance

Genetic Study — Variant c.581G>A (p.Arg194Trp) at exon 4 of the *PPAR-gamma gene*

2 40-year-old Caucasian woman



ENDOCRINOLOGY DEPARTMENT (10/10/2013)

Severe dyslipidemia - hypercholesterolemia and hypertriglyceridemia (15233 mg/dL)

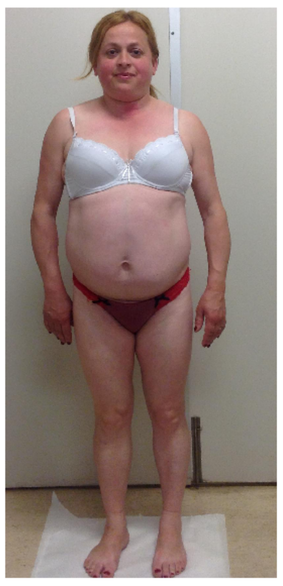
"Type 2" diabetes

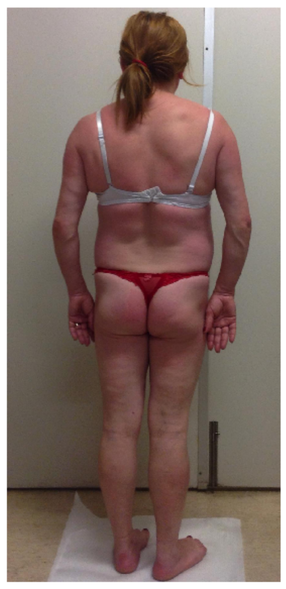
Diabetes mellitus since she was 22 years old, on insulin therapy for 10 years
*Diabetic retinopathy and nephropathy
Arterial hypertension
Depressive disorder
No history of pancreatitis or cardiovascular disease

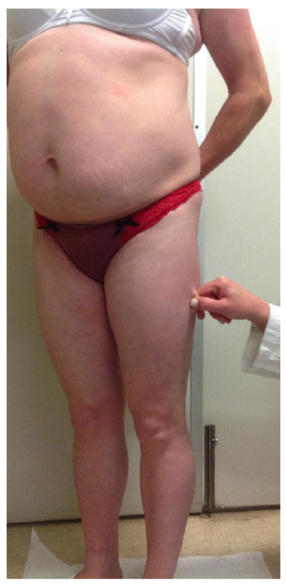
Medication
Insulin glargine 58 units at breakfast
Insulin aspart before meals (pre-meal goals 90-140 mg/dl, insulin sensitivity factor 40)
Rosuvastatin 10 mg once daily
Fenofibrate 267 mg once daily
Ramipril 5 mg once daily
Fluoxetine 20mg once daily

NON-COMPLIANCE WITH DRUG THERAPY

Physical Examination
Weight: 52.7 kg | Height: 1.47 m | BMI: 24.4 kg/m² | Waist circumference: 85 cm
BP 153/98mmHg, HR 105bpm
No acanthosis nigricans. No xanthomas, xanthelasmas or lipemia retinalis
Lipoatrophic extremities with muscular hypertrophy and vascular prominence; abdominal prominence and hepatomegaly







Laboratory tests
A1c **12.7%**
Total cholesterol **642** mg/dL; HDL cholesterol **90** mg/dL; LDL cholestrol **121** mg/dL; triglycerides **2404**mg/dL; apolipoprotein B **140** mg/dL (53-138); lipoprotein(a) **35.5** mg/dL (<30)
AST 25 U/L (10-31), ALT 21 U/L (10-31), GGT 23 U/L (7-32), FA 73 U/L (30-120)
Creatinine 0.39mg/dL (0.51-0.95); urine albumin-to-creatinine ratio **451,3**mg/g
TSH 1.33µUI/mL (0.35-4,94); T4L 0.79ng/dL (0.70-1.48)
Lipemic serum, with milky appearance

*Abdominal ultrasound: Hepatomegaly with steatosis (22cm)

Genetic Study — Variant c.581G>A (p.Arg194Trp) at exon 4 of the *PPAR-gamma gene*

Conclusion

The clinical features and biochemical profile suggested the diagnosis of genetic lipodystrophy, confirmed as FPL type 3. We underline the importance of clinical suspicion and early intervention of metabolic complications, in order to prevent early onset of cardiovascular disease and the occurrence of pancreatitis.