A 19 year follow-up of a woman with lipoprotein lipase deficiency treated with biliopancreatic diversion

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Key Clinical Message
We show the long-term efficacy and safety of modified biliopancreatic diversion for the treatment of LPL-deficiency. How this option compares with gene therapy is difficult to evaluate due to limited experience. Surgery may be the first option in patients in whom medical therapy is ineffective and gene therapy not applicable.

Keywords
Biliopancreatic diversion, hypertriglyceridemia, insulin resistance.

Introduction
Lipoprotein lipase (LPL) deficiency is a rare condition characterized by high plasma triglycerides, low HDL-cholesterol, and the presence of fasting chylomicrons due to a mutation of a key enzyme involved in the hydrolysis and removal of triglycerides from plasma [1]. Besides LPL, several additional loci have been identified, all of which encode for either cofactors or proteins involved in LPL’s maturation or binding to endothelium (APOC2, APOA5, GPI-HBP1, LMF1, GCKR) [2,3].

We report on the long-term follow-up of a 37-year-old woman with familiar chylomicronemia treated with modified biliopancreatic diversion (BPD). The diagnosis of LPL-deficiency was made at 13 years of age on the basis of cutaneous xanthomas, recurrent episodes of abdominal pain associated with increased serum amylase, very high triglyceride and documented low post-heparinic LPL activity (0.0015 μmol/mL/min). Missense mutations in exons 4 and 8 of LPL gene were detected in the patient, as reported in a previous publication by Mingrone et al. [4]. At the time of diagnosis, the patient was normal weight. Two years later, the patient developed diabetes mellitus, which was initially treated with metformin and subsequently with multiple insulin injections. At 18 years of age, because of persistent hypertriglyceridemia and poor glucose control despite high insulin dose (~2.7 UI/kg), the patient underwent modified Scopinaro’s BPD, as described in detail by Castagneto et al. [4]. Unlike the classical procedure performed in morbid obesity, in this case, a larger part of the stomach was maintained and the tract of absorbing intestine was half the length of the small bowel, in order to induce fat malabsorption while preventing excessive weight loss since the patient was normal weight (56 kg). Three weeks after surgery, glucose and lipids levels fell drastically; insulin therapy and hypolipidemic drugs were discontinued [5].

Over the years after intervention, the patient was in good health, her body weight ranged from 51 to 57 Kg. She had two pregnancies to term and a single first-trimester abortion; the babies were healthy and none was macrosomic. During both pregnancies, due to reoccurrence of diabetes, the patient was treated with insulin, which was discontinued after delivery.

In July 2014, she was referred to the Diabetes Clinic of the Department of Clinical Medicine and Surgery of Federico II University for a clinical assessment. She was taking metformin (1000 mg/die), \( ω \)-3 polyunsaturated fatty...
acids (3 g/day), vitamin, and mineral supplements albeit discontinuously. Blood tests showed elevated triglycerides (391 mg/dL) while liver and renal functions were normal. Glucose control was optimal (glycated hemoglobin, HbA1c was 5.2%); no sign of micro and macrovascular complications was detected. Computerized bone mineralometry dual-energy-X-Ray evidenced osteopenia. Ultrasonography showed enlargement of the liver and diffuse hepatic steatosis. No other nutritional deficiency was evident, except for a mild anemia.

In the light of the optimal glucose control, we decided to discontinue metformin and encouraged the patient to take ω-3 polyunsaturated fatty acids, multivitamin plus mineral supplements (containing iron, folic acid and vitamin B12, 1550 mg of calcium and 400 I.U. of vitamin D), and to follow a low-fat diet on a regular basis. Three months after metformin withdrawal, HbA1c was 4.3%. To better evaluate glucose homeostasis, the patient underwent a 75-g oral glucose tolerance test (OGTT) and a 1-week continuous glucose monitoring (CGM) (Table 1). Blood glucose was 391 mg/dL at T60' and 204 mg/dL at T120'. At CGM, the mean weekly blood glucose was 210 mg/dL with glucose nadir and peak of 115 and 400 mg/dL, respectively; more than 30% of the glucose values recorded were >200 mg/dL. Glycemic variability, expressed as mean daily standard deviation of blood glucose (SDglucose) was remarkably higher (64 mg/dL) than that reported in people with normal glucose tolerance (16/27 mg/dL) [6]. In addition, the stricter adherence to ω-3 polyunsaturated fatty acids and vitamin supplementation led to normalization of fasting triglycerides levels and normal nutritional status. Based on these findings, treatment with metformin was resumed.

LPL-deficiency is a rare monogenic disease with autosomal recessive transmission and a prevalence of 1-2:1,000,000 [1]; it is characterized by fasting chylomicronemia; recurrent, severe abdominal pain; increased risk of morbidities, such as pulmonary embolism-like syndrome; coronary heart disease with or without atherosclerosis and metabolic consequences of pancreatic insufficiency, including diabetes [1,7]. The most debilitating complication of the disease is recurrent and potentially life-threatening acute pancreatitis, as a consequence of chylomicrons hydrolysis in the pancreatic capillary bed with the formation of fatty acids and lysolecithin, which are thought to damage pancreatic cells.

Recurrent pancreatitis is associated with an increased incidence of pancreatic cancer and results in significant morbidity and mortality in 20–30% of patients, impacting the quality of life [7]. The treatment of LPL deficiency is generally based on severe restriction of dietary fat to 15–20% of total daily calories, associated with fibric acid derivatives and ω-3 fatty acids. Unfortunately, these measures are poorly effective in controlling hypertriglyceridemia and preventing the risk of complications.

The experience with surgical treatment is very limited. To our knowledge, our case was the first experience of BDP intervention for the treatment of LPL-deficiency. Subsequently, a similar procedure was successfully per-

### Table 1. Clinical, metabolic and nutritional status.

| Parameter                        | Value   |
|----------------------------------|---------|
| Body weight (Kg)                 | 51.3    |
| BMI (Kg/m²)                      | 21.1    |
| Waist circumference (cm)         | 82      |
| SBP/DBP (mmHg)                   | 110/80  |
| OGTT GlucoseT0 (mg/dL)           | 134     |
| OGTT GlucoseT60 (mg/dL)          | 391     |
| OGTT GlucoseT120 (mg/dL)         | 204     |
| Fasting insulin (µU/mL)          | 5       |
| Fasting C-peptide (nmol/L)       | 1.6     |
| HbA1c (%)                        | 4.3     |
| Total cholesterol (mg/dL)        | 114     |
| HDL-cholesterol (mg/dL)          | 38      |
| Triglycerides (mg/dL)            | 103     |
| OGIS (mL/min/m²)                 | 354     |
| HOMA-IR                          | 1.65    |

**Continuous Glucose Monitoring Data**

| Parameter                  | Value   |
|----------------------------|---------|
| Mean IG (mg/dL)            | 210     |
| Nadir IG (mg/dL)           | 115     |
| Peak IG (mg/dL)            | 400     |
| Standard deviation (mg/dL) | 64      |

BMI = body mass index; OGTT = oral glucose tolerance test; HDL = high density lipoprotein; OGIS = oral glucose insulin sensitivity; HOMA-IR = homeostasis model assessment-estimated insulin resistance; PCR = C-reactive protein; CGM = continuous glucose monitoring; IG = interstitial glucose.

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formed in a child [8], of whom 11-year follow up has been reported [9]. The patient was in good health with a near-normalization of plasma triglycerides. The present case report represents the longest follow up available to date and, together with the prior report [8], supports the efficacy and safety of modified BPD as a treatment option for LPL-deficiency.

Recently, gene therapy has become available for patients with mutations in the LPL gene but not in the cofactors (apoC2, apoA5 or GPI-HBP1) genes [7]. Promising results have been obtained with alipogene tiparvovec, an adeno-associated virus type I containing the LPL serine447-stop (S447X) gene construct. A single 2-year intervention study was conducted in 14 patients with mutations of LPL gene [10]. The intramuscular injection of alipogene tiparvovec resulted in transient 40% reduction in fasting triglycerides and sustained improvement in postprandial chylomicron triglycerides. A reduction in the number and severity of pancreatitis events was also observed in these patients compared with historic rates of pancreatitis associated with LPL-deficiency. Based on these data, in 2012, the drug was licensed for the treatment of chylomicronemia caused by mutations in the genes encoding LPL. Other alternative approaches to gene therapy are based on agents that reduce TG-rich particle synthesis at hepatic and enterocytes level. However, no studies in humans have been performed to date [11]. Due to the rarity of the disease and the limited experience with either surgical or gene therapy, a comparative cost-effectiveness evaluation of the two options is not feasible.

In this report, modified BPD was effective in controlling the symptoms and complications of LPL deficiency without major side effects in the long term. The clinical conditions of our patient, 19 years after modified BPD-induced lipid malabsorption, were overall satisfactory. She is maintaining normal body weight following a moderately hypolipidic diet, with plasma glucose and lipids within the target indicated by current guidelines.

As for diabetes, the surgical treatment has induced a significant improvement of the metabolic status, although a complete remission of diabetes was not achieved. An important observation emerging from these assessments is, in fact, the great discrepancy between the optimal HbA1c values, which would suggest normalization of glucose tolerance, according to current diagnostic criteria, and the CGM data that show large glucose fluctuations with several hyperglycemic peaks. Although this discrepancy may be partially explained by methodological factors (i.e., interference of hypertriglyceridemia and/or vitamin supplementation with HbA1c assay yielding falsely low values) [12], the finding underlines the limited value of HbA1c measurement for the evaluation and monitoring of glucose control in bariatric patients. This finding strengthens the need for blood glucose monitoring particularly in the postprandial period in order to reveal postprandial glucose peaks and glucose variability.

In conclusion, this case represents the longest follow-up in a patient undergoing surgical treatment for LPL deficiency. It documents durable efficacy and safety of modified Scopinaro’s BPD. How this option compares with gene therapy is difficult to evaluate due to the scanty data available so far. Surgery may be the first option in patients with chylomicronemia poorly controlled with traditional medical therapy and in those with mutations in the genes encoding LPL cofactors.

Conflict of Interest

None declared.

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