Effectiveness of Gastric Bypass Surgery in a Patient With Familial Partial Lipodystrophy

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Familial partial lipodystrophy (FPL) is associated with loss of subcutaneous fat in the extremities but preservation, or increase, of fat in the face, neck, and trunk. Patients with FPL manifest marked insulin resistance and develop diabetes and hypertriglyceridemia that are often very difficult to manage with pharmacologic agents, the current standard of therapy for FPL. Roux-en-Y gastric bypass (RYGB), a surgical procedure that leads to marked weight loss in morbidly obese subjects, improves insulin sensitivity (1,2) and reverses (3) or prevents diabetes (4). This is the first report of RYGB in a patient with FPL that resulted in unanticipated dramatic improvement in the metabolic control of her lipodystrophy.

HISTORY AND EXAMINATION

The patient is a 55-year-old Caucasian woman with FPL who underwent a laparoscopic RYGB for treatment of severe gastroesophageal reflux disease and gastroparesis, failing standard medical therapy. She reported a history of truncal obesity and thin extremities throughout her life. She was diagnosed with FPL type 1 based on physical exam findings of distal loss of subcutaneous fat in her extremities with excess fat in her chin and face and marked abdominal obesity. Her medical problems included poorly controlled type 2 diabetes, hypertriglyceridemia with a history of recurrent pancreatitis, coronary artery disease, hypertension, depression, and asthma. Her family history was significant for early coronary artery disease in her mother. She did not smoke and denied alcohol intake. On physical examination, her weight was 90.2 kg (BMI 33.1 kg/m^2) and her blood pressure was 120/70 mmHg on amlodipine, furosemide, enalapril, and diltiazem.

Preoperative samples were collected in 2001 as part of a study of lipodystrophy, and postoperative samples were obtained ~16 months after surgery for analysis of insulin, leptin, and adiponectin. The subject provided written informed consent.

INVESTIGATION

Before RYGB, she showed marked insulin resistance. Despite rosiglitazone and >300 units insulin/day, her diabetes was poorly controlled. Triglycerides ranged from 1,700 to 3,500 mg/dl (19.1 to 39.3 mmol/l) on treatment with fenofibrate 160 mg q.d. (Fig. 1).

After surgery, weight decreased gradually and she tapered herself off insulin completely over the following 2 months. Rosiglitazone was discontinued 6 months later. On follow-up, she was noted to have lost weight, specifically in her face and abdomen. A year and a half after the procedure, she had lost 30% of her preoperative body weight. Her blood pressure decreased, and she reduced her antihypertensive medication. Sixteen months after surgery, her triglycerides and diabetes were well controlled while off all diabetes and lipid medications, although her HDL cholesterol remained low (Fig. 1). Liver enzymes were unremarkable before and following RYGB.

In addition to an improvement in HbA_{1c} (A1C), fasting insulin levels fell (48.4 to 5.4 μU), consistent with a dramatic improvement in insulin sensitivity. In keeping with her weight loss, leptin decreased by >50% (10.1 to 4.0 ng/ml) but adiponectin remained low (2.7 before and 3.7 μg/ml after).

CONCLUSIONS

The mechanisms underlying insulin resistance in the various forms of lipodystrophy are not clear. Generalized lipodystrophy is associated with loss of subcutaneous fat and variable loss of intraperitoneal fat and has been associated with low levels of the adipokines leptin and adiponectin, consistent with the overall lack of adipose tissue (5). Leptin acts centrally to improve insulin sensitivity (6), and adiponectin is positively associated with insulin sensitivity and negatively associated with intra-abdominal fat (7). Animal models of generalized lipodystrophy demonstrate significant insulin resistance and diabetes that can be reversed by subcutaneous fat transplantation (8), overexpression of leptin (9), or replacement of both leptin and adiponectin (10). Treatment of lipodystrophy with recombinant leptin in humans results in improved glycemic control and lowering of triglycerides (11). While these data suggest that a lack of adipose tissue hormones may be responsible for insulin resistance in generalized lipodystrophy, this mechanism is unlikely to underlie the remarkable reversal of insulin resistance seen in our patient, as her leptin level fell and her adiponectin level rose only minimally.

Insulin resistance is more strongly associated with intra-abdominal fat than subcutaneous fat (12), and FPL is characterized by loss of peripheral subcutaneous fat but the presence of truncal obesity. In contrast, acquired partial lipodystrophy is characterized by the loss of subcutaneous fat in a cephalocaudal sequence, including loss of fat from the thorax and abdomen with

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Received for publication 18 January 2006 and accepted in revised form 3 March 2006.

Abbreviations: FPL, familial partial lipodystrophy; GLP-1, glucagon-like peptide 1; RYGB, Roux-en-Y gastric bypass.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0130

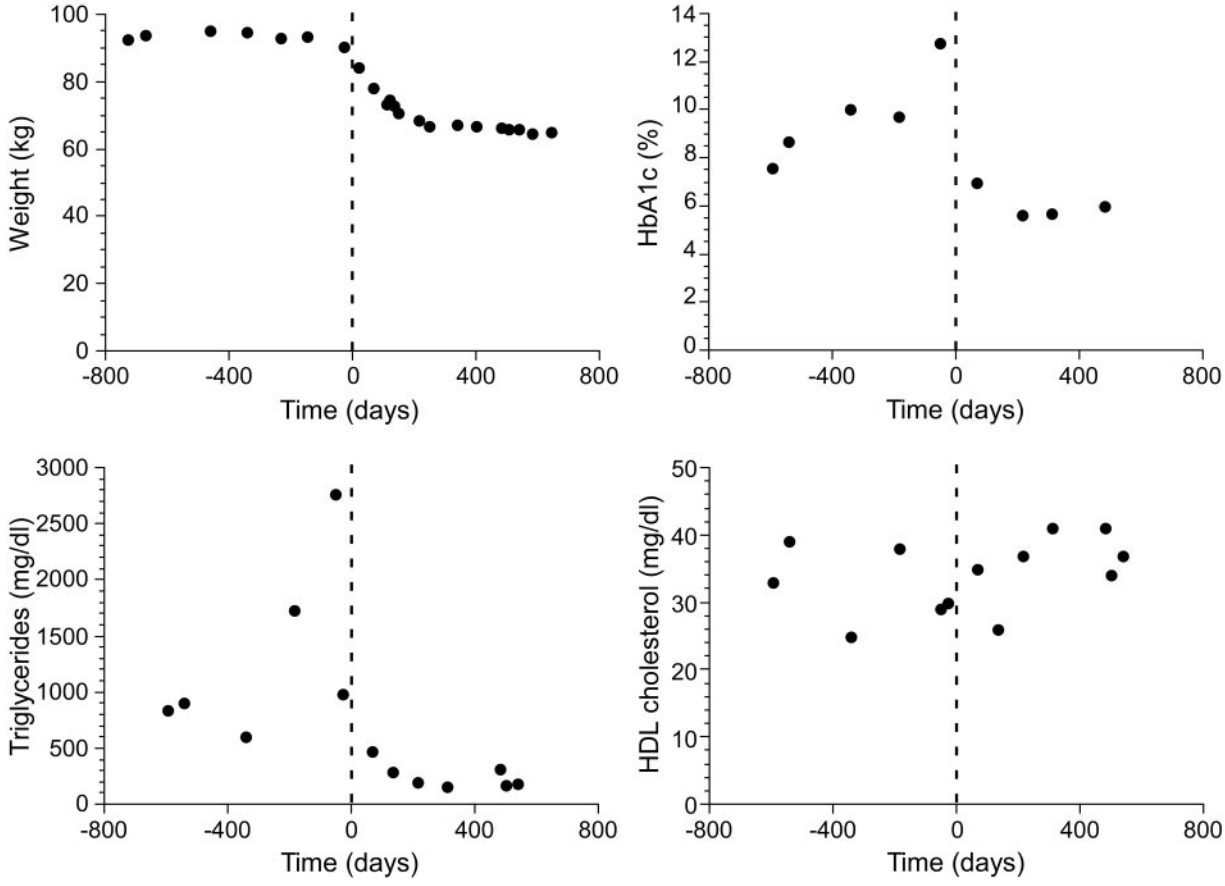

Figure 1—*Weight, HbA$_{1c}$ (A1C), triglyceride, and HDL cholesterol levels are depicted over time before and after RYGB performed on day 0. Weight decreased gradually after surgery and then stabilized. Both A1C and triglyceride levels decreased after RYGB, and HDL cholesterol increased slightly.*

sparing of the lower extremities, and insulin resistance is uncommon (13). These observations suggest that it may be the relative increase in truncal fat, rather than simply an absence of fat, that mediates insulin resistance in FPL. Thus, loss of intra-abdominal fat accompanying weight loss after RYGB may have contributed to the improvement in insulin sensitivity and metabolic control in our patient.

However, the mechanisms underlying the dramatic effects of RYGB on diabetes control and triglycerides are not fully known. Part of the effect undoubtedly results from weight loss and reduction of fat deposits that cause or contribute to insulin resistance. Reduced nutrient intake, independent of its effects to decrease body weight, can also result in improved glucose and triglyceride levels (14). A third hypothesis is that bypass of the foregut may directly control glucose metabolism, independent of weight loss or treatment of obesity, possibly by altering gut hormonal and/or neural signals, such as increased glucagon-like peptide 1 (GLP-1), decreased ghrelin, and perhaps alterations in foregut factors that have yet to be discovered (15). Whether the resolution of diabetes following RYGB in this case was solely due to weight loss with loss of abdominal adipose tissue, a negative caloric balance, or from other mechanisms, such as altered gastrointestinal hormones, is not yet clear. However, gastric bypass, even in the absence of morbid obesity, may present an alternative treatment for those patients with FPL who have severe metabolic manifestations that cannot be controlled with pharmacologic therapy.

Acknowledgments— This work was supported by National Institutes of Health Grant M01-RR-00037 and by National Institute of Diabetes and Digestive and Kidney Diseases Metabolism Training Grant T32 DKO7247.

We acknowledge the work of Dr. Karen Herbst, who collected the initial data, and thank Drs. John Brunzell and David Cummings for their assistance.

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