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Obesity and Insulin Resistance in Type 1 Diabetes Mellitus: From Bariatric Surgery to Pancreas Transplantation

Kathryn Capalbo, BSc,[1] Jenny M. Ngo, MD,[2,3] Susan L. Karam, MD,[4] Humberto Bohorquez, MD[1,2,3]

[1]The University of Queensland Medical School, Ochsner Clinical School, New Orleans, LA [2]Multi-Organ Transplant Institute, Ochsner Clinic Foundation, New Orleans, LA [3]Xavier Ochsner College of Medicine, New Orleans, LA [4]Department of Endocrinology, Ochsner Clinic Foundation, New Orleans, LA

Background: Obese patients with type 1 diabetes mellitus can develop insulin resistance. While medical therapy to treat insulin resistance in patients with type 1 diabetes mellitus is often limited, bariatric surgery has been used to promote weight loss and to improve insulin sensitivity. However, postoperative bariatric surgery outcomes reported for some patients with type 1 diabetes mellitus have included insufficient glycemic control and hypoglycemia.

Case Report: A female patient who had been diagnosed with type 1 diabetes mellitus at age 20 years developed morbid obesity and medically refractory insulin resistance over a 20-year period. She underwent bariatric surgery at age 42 years, achieving substantial weight loss (body mass index of 21 kg/m^2) and improved insulin resistance. Despite this improvement, the patient continued to experience poor glycemic control and began to have recurrent episodes of hypoglycemia despite receiving maximal medical therapy. At age 49 years, she underwent pancreas transplantation that restored glucose regulation.

Conclusion: In select obese patients with type 1 diabetes mellitus, insulin resistance, and poor glycemic control, bariatric surgery followed by pancreas transplantation may offer a viable pathway to reduce weight, improve insulin sensitivity, and restore glucose homeostasis.

Keywords: *Bariatric surgery, insulin resistance, obesity, pancreas transplantation*

Address correspondence to Humberto Bohorquez, MD, Multi-Organ Transplant Institute, Ochsner Clinic Foundation, 1514 Jefferson Hwy., New Orleans, LA 70121. Tel: (504) 842-3925. Email: hbohorquez@ochsner.org

INTRODUCTION

Insulin resistance, once considered to be associated exclusively with type 2 diabetes mellitus, can also occur in patients with type 1 diabetes mellitus.[1] Insulin resistance is strongly associated with overweight and obesity.[2] As obesity has become more prevalent among patients with type 1 diabetes mellitus (with rates ranging from 2.8% to 37.1% in various studies), the prevalence of insulin resistance is expected to rise accordingly.[3] Insulin resistance adds further challenges in the management of type 1 diabetes mellitus, an already-complex condition because of the deficit of insulin.[1,2]

Medical therapies used to treat insulin resistance in patients with type 2 diabetes mellitus have been applied to patients with type 1 diabetes mellitus, but clinical experience is limited and outcomes are inconsistent.[4] Bariatric surgery is an option for weight reduction and improves insulin sensitivity. However, postoperative complications—including worsening glycemic instability, ketoacidosis, and hypoglycemia—have been documented in patients with type 1 diabetes mellitus who have undergone bariatric surgery.[5]

We present a case that illustrates the clinical course and management challenges of a patient with type 1 diabetes mellitus and insulin resistance who underwent pancreas transplantation after bariatric surgery.

CASE REPORT

A female patient was diagnosed with type 1 diabetes mellitus at age 20 years. Her father, both paternal aunts, and a maternal aunt had diabetes, although the types were unclear. During the following decades, the patient became morbidly obese and developed progressive insulin resistance that was refractory to medical therapy. By age 39 years, her body mass index (BMI) was 35 kg/m^2, and her diabetes remained poorly controlled despite multiple insulin protocols and delivery pumps, including Humulin R U-500 with a Medtronic insulin pump, dulaglutide 1.5 mg every week, insulin degludec 14 U subcutaneously daily, and metformin extended-release 1,000 mg twice daily. The patient's HbA1c remained >9% despite maximum therapy, and she began experiencing recurrent hypoglycemia.

At age 42 years, with a BMI of 37.6 kg/m^2, the patient underwent laparoscopic Roux-en-Y gastric bypass surgery. By 14 months postoperatively, her BMI had decreased to 21 kg/m^2 and she achieved temporary glycemic stability with continuous glucose monitoring and dulaglutide 1.5 mg

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weekly. This regimen was transitioned 2 months later to a t:slim insulin pump (Tandem Diabetes Care, Inc) with Control-IQ+ delivering Humalog U-100. Six months after her bariatric surgery, the patient again developed frequent hypoglycemia. Given the patient's persistent glycemic instability, her high risk of progressive diabetic complications, and the failure of multiple medical therapies, she was referred to our center for evaluation for pancreas transplantation.

At the age of 49 years, with a BMI of 19 kg/m^2 and preserved renal function (glomerular filtration rate >80 mL/min), the patient underwent pancreas transplantation alone with systemic venous drainage and enteric drainage via duodenoduodenostomy. Immunosuppression included thymoglobulin induction and maintenance therapy with tacrolimus, mycophenolate, and prednisone. The pancreas allograft demonstrated immediate function, and the patient became insulin independent with complete resolution of hypoglycemia. One year after pancreas transplantation, the patient's BMI was 23 kg/m^2, HbA1c was 5.3%, and C-peptide level was 4.9 ng/mL.

DISCUSSION

Although insulin deficiency is the defining feature of type 1 diabetes mellitus, insulin resistance is increasingly recognized in this population.[1] Patients with type 1 diabetes mellitus who have a family history of diabetes mellitus, exhibit features of type 2 diabetes mellitus such as obesity and metabolic syndrome, and develop insulin resistance are described as having double diabetes, hybrid diabetes, or type 1.5 diabetes.[6] This symptom overlap suggests that type 1 and type 2 diabetes mellitus are on a spectrum of the same disease rather than 2 distinct entities.[6] Patients with type 1 diabetes mellitus who develop insulin resistance are at increased risk of diabetic complications and mortality, independent of their average glucose control or HbA1c level, likely because of the microvascular burden.[7,8]

The pathogenesis of insulin resistance in type 1 diabetes mellitus is not well understood but appears to be multifactorial and to involve lifestyle factors, genetic predisposition, repeated hypoglycemia, and the nonphysiologic nature of subcutaneous insulin administration.[9] Attempts to achieve optimal glycemic control by intensifying insulin therapy in obese patients with type 1 diabetes mellitus may trigger a cycle of hypoglycemia, compensatory carbohydrate intake, rebound hyperglycemia, and escalating insulin doses—ultimately worsening weight gain and insulin resistance.[4,9] Additional mechanisms that may contribute to weight gain include increased sympathetic nervous system activity, altered protein turnover, changes in substrate transport, alterations in the gut microbiome, and an increase in the size of metabolically active organs.[1,2]

Management of insulin resistance in obese patients with type 1 diabetes mellitus is challenging. The traditional strategies of insulin optimization, nutrition, exercise, and lifestyle modifications often fail to achieve adequate glycemic control. Medications used to treat insulin resistance in patients with type 2 diabetes mellitus (metformin, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors) may reduce weight, improve hyperglycemia, and have beneficial cardiovascular effects, but concerns about diabetic ketoacidosis, hypoglycemia, costs, off-label use, and minimal long-term efficacy limit their routine use in patients with type 1 diabetes mellitus.[1,2]

Bariatric surgery outcomes in patients with type 1 diabetes mellitus have not been evaluated in randomized controlled trials, but experience in several cohorts of patients with type 1 diabetes mellitus has been reported. In a 2020 review, Korakas et al summarize the effects of bariatric surgery on weight loss, daily insulin requirements, and HbA1c in obese patients with type 1 diabetes mellitus.[5] In 189 patients from 20 studies who had obesity and type 1 diabetes mellitus and underwent bariatric surgery—Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric band, or biliopancreatic diversion—mean BMI reductions ranged from 8.3 to 23 kg/m^2. Although insulin requirements decreased, the effect on glucose control and HbA1c was modest or nonexistent.[5] In a 2019 review, Yeung et al reported beneficial effects of bariatric surgery on insulin requirements and HbA1c reduction but limited improvement of daily glucose control.[10] These mixed results highlight the metabolic heterogeneity across the diabetes types.

Reports describe minimal major complications after bariatric surgery.[5,10,11] Notably, in patients with type 1 diabetes mellitus, bariatric surgery was associated with increased rates of diabetic ketoacidosis and hypoglycemia.[11] Rapid carbohydrate delivery to the jejunum after Roux-en-Y gastric bypass combined with improved insulin sensitivity may create a mismatch between glucose absorption and exogenous insulin action, contributing to severe hypoglycemia. For that reason, sleeve gastrectomy may be a more appropriate option for patients with type 1 diabetes mellitus.[10]

Pancreas transplantation is the most effective intervention for restoring glucose homeostasis and preventing progression of complications. However, organ scarcity, surgical risk, and lifelong immunosuppression limit transplantation.[12] Additionally, pancreas transplantation is generally restricted to patients with a BMI <30 kg/m^2, so substantial weight loss is necessary for obese candidates to qualify.[13]

Data on pancreas transplantation outcomes after bariatric surgery are limited. Porubsky et al reported on 4 morbidly obese patients (BMI of 38 to 59.8 kg/m^2) with type 1 diabetes mellitus and severe recurrent hypoglycemia who underwent bariatric surgery (3 Roux-en-Y gastric bypass and 1 sleeve gastrectomy) followed by pancreas transplantation 1.7 to 7.6 years later.[13] All patients had an unremarkable postoperative course and achieved stable glucose control and resolution of hypoglycemia.[13] Matar et al identified 17 patients who received a pancreas transplant after bariatric surgery (1.1% of 1,542 total pancreas transplant patients); the outcomes of the patients who had undergone bariatric surgery were comparable to the outcomes of the patients who did not undergo bariatric surgery.[14] Matar et al noted transplant challenges because of the altered anatomy after bariatric surgery and used a side-to-side jejunal anastomosis technique.[14] In our case, we used a duodenoduodenostomy to provide more physiologic drainage and to facilitate postoperative management.

Islet transplantation is an alternative to whole pancreas transplantation in patients with type 1 diabetes mellitus and preserved renal function. However, inferior long-term outcomes, the need for more than one islet infusion in

approximately 70% of cases, and the fact that few medical centers offer this therapy limit the application of islet transplantation.[15]

CONCLUSION

In select obese patients with type 1 diabetes mellitus, insulin resistance, and difficult glycemic control, bariatric surgery followed by pancreas transplantation may offer a viable pathway to achieve weight reduction, improve insulin sensitivity, and restore glucose homeostasis.

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