Good Glycemic Outcomes Following Bariatric Surgery Among Patients With Type 2 Diabetes, Obesity, and Low-Titer GAD Antibodies

Ruveena Kaur,[1] David Kim,[2] Richard Cutfield,[2] Michael Booth,[3] Lindsay Plank,[4] and Rinki Murphy[1,5,6]

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OBJECTIVE

To evaluate diabetes remission after bariatric surgery by presence of GAD antibody among those with obesity and type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

Screening GAD was performed in 221 patients with T2D and obesity referred for bariatric surgery. Nine of 16 patients with GAD and 112 of 205 without GAD proceeded with surgery. Diabetes remission and weight loss were compared by GAD presence.

RESULTS

The group with GAD had levels 16–91 IU/mL. Those with and without GAD were similar with regard to age, BMI, diabetes duration, proportion treated with insulin, HbA_{1c}, and C-peptide (1,354 ± 548 vs. 1,358 ± 487 pmol/L). At 1 and 5 years postoperatively, the two groups achieved similar BMI reduction and diabetes remission (67% vs. 73%, $P = 0.71$, and 56% vs. 57%, $P = 1.0$).

CONCLUSIONS

Low-titer GAD in patients with T2D and retained C-peptide should not be a deterrent for bariatric surgery when the principal aim is diabetes remission.

Bariatric surgery achieves long-term weight loss and remission of type 2 diabetes (T2D) (1,2). Given resource limitations, patients are often prioritized by clinical characteristics associated with greatest likelihood of diabetes remission following bariatric surgery.

Latent autoimmune diabetes of adults (LADA) is a form of adult-onset autoimmune diabetes that fails to remit following bariatric surgery (3,4) and may be misclassified as T2D. Standard definitions for LADA are lacking, but the Immunology of Diabetes Society has proposed three criteria: *1*) age usually >30 years, *2*) no treatment with insulin within the first 6 months after diagnosis, and *3*) positive titer for at least one of the four autoantibodies (5). Antibody to GAD is the most commonly tested diabetes autoantibody, which is considered a marker of cellular-mediated destruction of β-cells (6,7). GAD is also the most frequent of the four antibodies that are detectable in both LADA and type 1 diabetes (T1D), although other antibodies, to islet antigen 2 (IA2), insulin autoantibody, or zinc transporter 8, may also be present (5,8). Both higher titers of GAD and lower

[1]*Diabetes Centre, Greenlane Clinical Centre, Auckland District Health Board, Auckland, New Zealand*
[2]*Diabetes Centre, North Shore Hospital, Waitemata District Health Board, Auckland, New Zealand*
[3]*Department of Surgery, North Shore Hospital, Waitemata District Health Board, Auckland, New Zealand*
[4]*Department of Surgery, University of Auckland, Auckland, New Zealand*
[5]*Department of Medicine, University of Auckland, Auckland, New Zealand*
[6]*Maurice Wilkins Centre for Biodiscovery, University of Auckland, Auckland, New Zealand*

Corresponding author: Rinki Murphy, r.murphy@auckland.ac.nz

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levels of plasma C-peptide (a marker of endogenous insulin production) have been associated with earlier insulin requirement among those with LADA, although variable definitions of high levels of GAD or low C-peptide have been used (9,10).

It is unclear whether routine autoantibody screening should be undertaken preoperatively in obese T2D patients, to detect misclassified LADA, in whom persistent diabetes after bariatric surgery is expected, which should be appropriately managed with insulin for avoidance of ketoacidosis (1). We hypothesized that those with clinically classified T2D and preserved C-peptide would benefit from diabetes remission after bariatric surgery irrespective of GAD antibody status.

RESEARCH DESIGN AND METHODS

Screening GAD and IA2 antibody testing was performed in 221 clinically diagnosed T2D patients with morbid obesity (BMI 35–65 kg/m^2) as part of baseline screening for eligibility to participate in a randomized blinded trial of diabetes remission following silastic ring laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy in Auckland, New Zealand (1). Informed consent was obtained from all participants. The study was approved by the New Zealand Health and Disability Ethics Committee.

Prospective clinical data were collected on all those who underwent bariatric surgery, including age, duration of diabetes diagnosis, BMI, HbA_{1c}, diabetes treatment, and diabetes autoantibody levels. Postprandial C-peptide was measured with use of the chemiluminescent method (normal range 350–750 pmol/L). GAD (normal <10 IU/mL) and IA2 (normal <10 IU/mL) autoantibodies were measured with the EUROIMMUN ELISA assay (11). Only those with C-peptide >350 pmol/L were accepted for bariatric surgery.

We performed statistical analysis using means and SDs for normally distributed data and medians and interquartile ranges for non–normally distributed data. Categorical data were analyzed with Fisher exact test. Post hoc power analysis showed that there was 80% power to detect a 60% difference in proportion achieving diabetes remission between the two groups (9 GAD-positive vs. 98 GAD-negative patients), defined as HbA_{1c} <48 mmol/mol (<6.5%) without the need for glucose-lowering medications.

RESULTS

Of the 221 patients with T2D and obesity considering bariatric surgery, 16 were found to have GAD antibodies, of whom 9 received surgery. Of the 205 patients without GAD antibodies, 112 received bariatric surgery. Reasons for not proceeding with surgery included personal preference, surgical contraindications, or reclassification as having T1D in two cases, due to high-titer GAD (>180 IU/mL) and basal-bolus insulin requirement.

In those who proceeded with surgery, preoperative GAD antibody concentrations ranged from 16 to 91 IU/mL (normal <10 IU/mL) (Supplementary Table 1). Only one had dual GAD (31 IU/mL) and IA2 antibodies (109 IU/mL), but the patient remained without insulin treatment prior to bariatric surgery 10 years after diabetes diagnosis. Two were insulin treated (after 2.8 and 5 years following diabetes diagnosis). One had a history of Graves' thyrotoxicosis. Those with GAD antibodies had similar age, BMI, HbA_{1c}, and C-peptide compared with those without GAD (Table 1). At 1 and 5 years after surgery, both groups achieved similar diabetes remission and mean reduction in BMI (Table 1).

CONCLUSIONS

This study demonstrates that the presence of GAD antibodies has no significant impact on diabetes remission rates after bariatric surgery among those with clinically classified T2D, obesity, and preserved C-peptide (>680 pmol/L). Such cases are distinct from typical LADA cases, where there is persistent diabetes and risk of diabetic ketoacidosis after bariatric surgery (4). This highlights the need for precision in classifying diabetes subtype, which is inadequately marked by the presence of GAD antibodies alone in defining LADA.

Detailed characterization of LADA with preoperative insulin requirement, GAD titer, and C-peptide has not been reported in bariatric surgery literature to date. A case series of 10 patients with obesity and LADA (defined by presence of GAD antibodies) described persistent need for insulin treatment, without improvement in HbA_{1c}, after bariatric surgery. Only 2 of these 10 patients were reported to have detectable C-peptide at time of surgery, and 4 patients developed diabetic ketoacidosis in the first postoperative month (4). In a case report of a 43-year-old woman, with clinically diagnosed T2D (insulin commenced 2 years after diagnosis), who demonstrated worsening glycemic control 1 year following silastic ring laparoscopic Roux-en-Y gastric bypass surgery and had high-titer GAD antibodies (>2,000 IU) when tested postoperatively, the woman was retrospectively diagnosed with LADA. C-peptide had not been measured preoperatively (3). The utility of preserved C-peptide preoperatively in prediction of good diabetes remission following bariatric surgery has not previously been reported among LADA patients.

Routine screening for GAD among 221 people with obesity and T2D considering bariatric surgery at our center identified 6% of case subjects with a positive result ($n = 16$), one of whom had dual GAD and IA2 antibodies. Only two had high-titer GAD (>180 IU/mL), both of whom were reclassified as having T1D and did not proceed with bariatric surgery. These results are consistent with antibody studies among people with T2D without morbid obesity. In 4,250 patients with clinically classified T2D and no prior insulin treatment, 4.4% were found to be GAD antibody positive ($n = 191$), 0.91% IA2 antibody positive ($n = 39$), and 0.87% dual antibody positive ($n = 37$) (10). Those with detectable antibodies were reclassified as having LADA, of whom a higher proportion of those with high-titer GAD (>32 GAD units) became insulin deficient, suggesting a more severe phenotype (10). However, variable thresholds and assays have been used to define high-titer GAD and its association with more rapid β-cell failure than is characteristic of T2D, such as 174 units/mL (12) or 180 units/mL (9).

The small sample size of GAD-positive case subjects is a key limitation. However, this study indicates reassuringly high diabetes remission among this subset of patients with LADA after bariatric surgery, in contrast to all other reports of patients with LADA to date describing persistent diabetes and risks of ketoacidosis after surgery. Another limitation is the two different types of bariatric surgery used. Nonetheless, there were similar proportions allocated to either type of surgery in both groups.

In conclusion, low-titer GAD antibodies (<100 IU/mL) along with preserved C-peptide (>680 pmol/L) should not be

Table 1—Baseline characteristics and metabolic outcomes of patients receiving bariatric surgery by GAD status

	GAD positive	GAD negative	*P*
Preoperative characteristics	*N* = 9	*N* = 112	
Age, years	48.8 ± 3.3	46.8 ± 6.6	0.38
Female sex, *n* (%)	5 (56)	58 (52)	1.00
Duration of diabetes, years	7.7 ± 5.4	6.8 ± 5.3	0.60
Use of insulin, *n* (%)	2 (22)	33 (29)	1.00
HbA_{1c}, mmol/mol	58.3 ± 11.3	63.4 ± 15.7	0.38
HbA_{1c}, %	7.5 ± 1.0	8.0 ± 1.4	0.38
C-peptide, pmol/L*	1,354 ± 548	1,358 ± 487	0.98
C-peptide range, pmol/L*	687–2,330	490–3,140	
Body weight, kg	125.8 ± 24.6	125.3 ± 23.0	0.96
BMI, kg/m^2	44.6 ± 7.8	42.5 ± 6.3	0.36
RYGB surgery type, *n* (%)	4 (44)	55 (49)	1.00
SG surgery type, *n* (%)	5 (56)	57 (51)	
1-year postoperative outcomes	*N* = 9	*N* = 107	
HbA_{1c} <48 mmol/mol or <6.5% without diabetes medication, *n* (%)	6 (67)	78 (73)	0.71
Body weight, kg	88.5 ± 13.2	86.7 ± 17.0	0.75
Change in body weight from baseline, kg	−37.2 ± 18.6†	−37.1 ± 12.5†	0.97
Percentage change in body weight from baseline, %	−28.5 ± 10.0†	−29.8 ± 7.9†	0.63
BMI, kg/m^2	31.7 ± 6.0	29.4 ± 4.6	0.17
Change in BMI from baseline	−12.9 ± 5.5†	−12.7 ± 4.2†	0.89
5-year postoperative outcomes	*N* = 9	*N* = 98	
HbA_{1c} <48 mmol/mol (<6.5%) without diabetes medication, *n* (%)	5 (56)	56 (57)	1.00
Body weight, kg	96.1 ± 18.3	95.9 ± 18.5	0.98
Change in body weight from baseline	−29.6 ± 25.2†	−26.5 ± 14.1†	0.56
Change in body weight percentage from baseline	−21.9 ± 17.2†	−21.4 ± 9.7†	0.89
BMI, kg/m^2	34.6 ± 8.4	32.8 ± 5.4	0.37
Change in BMI from baseline	−10.0 ± 8.0†	−9.1 ± 4.7†	0.61

Data are mean ± SD unless otherwise specified. RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy. *C-peptide reference range 370–1,470 pmol/L. †$P < 0.01$ for changes from baseline.

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