Bariatric Surgery Outcomes in Patients with Latent Autoimmune Diabetes of the Adult

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Abstract

Bariatric surgery is a very effective treatment for obesity-associated type 2 diabetes. However, the benefits of bariatric surgery in patients with obesity and autoimmune diabetes, such as type 1 diabetes and latent autoimmune diabetes in adults (LADA), are controversial. We report 3 female patients with obesity and LADA who underwent laparoscopic Roux-en-Y gastric bypass >10 years ago. The patients were diagnosed with LADA both 1 and 9 years before (\(n = 2\)) or 11 years after the surgery (\(n = 1\)). Patients preoperative body mass index ranged from 36 to 47 kg/m\(^2\) and improved to 23–37 kg/m\(^2\) in the last follow-up visit, 10–15 years after surgery. Daily insulin dose also decreased from an average of 0.68 to 0.45 IU/kg in those patients treated with insulin before bariatric surgery. Only one patient developed diabetes-related target organ damage. This study shows that patients with LADA depict remarkable reduction of body weight and insulin requirements over long-term after bariatric surgery. So, LADA should not be considered a contraindication for bariatric surgery yet should only be recommended for patients with concomitant obesity with the primary aim of achieving sustained weight loss.

Introduction

Latent autoimmune diabetes of adult (LADA) was first described in 1986 by Groop et al. [1] after detecting the presence of antibodies against pancreatic β-cell structures in adult patients with diabetes. LADA diagnosis relies on uncovering the existence of circulating autoantibodies anti-glutamic acid decarboxylase 65 (anti-GAD) and islet cell antibodies (ICA), with or without the presence of typical type 1 diabetes (T1D) autoantibodies, such as insulin autoantibodies and IA-2 in adult patients with insulin-dependent diabetes [2]. According to the Immunology of Diabetes Society (IDS), 3 criteria are required for LADA definition: (1) age ≥30 years, (2) positive titers of at least one of the 4 autoantibodies described as associated with autoimmune diabetes, and (3) no requirement of insulin treatment in the first 6 months of diagnosis [3].
As LADA prevalence among the type 2 diabetes (T2D) patient population can range between 4 and 12%, there is an estimated number of 17–50 million people affected worldwide [4]. LADA is characterized by a mild autoimmune process slowly leading to progressive insulin deficiency as compared to T1D that occasionally runs together with overweight and insulin resistance, which characterize T2D [5]. Data from cross-sectional studies suggest that individuals with LADA tend to have an intermediate body mass index (BMI) between those of subjects with T1D and T2D [6]. Moreover, overweight when combined with HLA risk genotypes can confer an eightfold higher risk of LADA [7]. Two different LADA subtypes have been so far described. Type 1 LADA presenting with at least 2 different positive autoantibodies, including anti-GAD and ICA, characterized by greater insulin deficiency, lower BMI, and lower incidence of cardiovascular complications, resembling T1D. Type 2 LADA that presents positivity for one single autoantibody, and a similar phenotype and cardiovascular risk profile as observed for patients with T2D [8]. However, regardless of the subtype classification, individuals diagnosed with LADA are very heterogeneous in genetic, pancreatic β-cell destruction rate, and phenotypic and immunological features, such as insulin resistance and autoimmunity [9, 10]. The fact that autoimmunity in LADA seems less pronounced while overweight and obesity are more frequent than observed in T1D suggests that insulin resistance could also play a role by increasing β-cell demand and failure. Indeed, overweight and obesity were shown to be associated with an increased risk of LADA, and the risk seems to be highest in individuals with family history of diabetes [6].

In a large meta-analysis of bariatric surgery outcomes in patients with T1D, LADA was identified to be present in 3.3% of the subjects [11]. After bariatric surgery, patients with LADA can experience initial diabetes remission followed by relapse. This observation led the authors to hypothesize that insulin resistance could play a key role in promoting autoimmune diabetes, further suggesting that T1D and T2D could share some mechanisms of disease driven by insulin resistance, although set against a different genetic background [12].

There are no specific treatment guidelines for LADA [13], management of which tends to be similar to those of patients with T1D or T2D with fully established β-cell failure [14]. The treatment goals for LADA are to obtain good glycemic control and prevent or delay diabetes complications. Patients with LADA may transiently respond to non-insulin antidiabetic drugs but often require insulin therapy within 5 years of diagnosis [15].

Morbidity and mortality rates of patients with LADA tend to be as high as those of patients with T2D and mostly driven by cardiovascular disease, despite the more favorable metabolic parameters. In the HUNT study (Norwegian Nord-Trøndelag Health Study), the largest population-based study on autoimmune diabetes (including LADA), hyperglycemia was shown to be the only factor with a significant influence on mortality [16–18]. In addition, in the BOTNIA study, patients with LADA with a disease duration over 5 years had an increased risk of retinopathy and neuropathy than observed for patients with T2D [19]. Moreover, recent evidence suggests that glycemic instability could play an even greater role than HbA1c in the development of diabetes complications [20].

In contrast to T2D, T1D and LADA are not recognized as metabolic disorders amenable for bariatric surgery treatment. Nevertheless, the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) has recently stated that patients with T1D and severe obesity could be considered for obesity surgery treatment [21]. The aim of this study was to describe the long-term outcomes of a small cohort of patients with obesity and LADA submitted to bariatric surgery.

**Case Report**

Between November 2005 and October 2010, 3 female patients, with a median age of 35 years (range 25–42), underwent laparoscopic Roux-en-Y gastric bypass (RYGB) for the primary treatment of obesity. The need for written informed consent by the patients was waived by the Ethics Committee, as part of a larger retrospective study (approval number: CA-149/2020-0t_MP/AC). The patients were diagnosed with diabetes either before bariatric surgery (n = 2) or after bariatric surgery (n = 1). LADA diagnosis was established by the presence of positive anti-GAD antibodies and insulin treatment requirement for glycemic control.

Patient A was diagnosed with diabetes at 29 years with positive anti-GAD and ICA. The patient underwent RYGB surgery 9 years after LADA diagnosis with a BMI of 36 kg/m² and poor glycemic control with an HbA1c 7.3%. Surgery was successful in achieving sustained weight loss up to 10 years of follow-up.

Patient B was diagnosed with insulin-requiring diabetes at 24 years with positive anti-GAD and ICA. The patient was submitted to RYGB surgery 1 year after LADA diagnosis with a BMI of 38 kg/m² and labile glycemic control with frequent hyper- and hypoglycemic episodes under intensive insulin treatment with multiple daily injections. After surgery the patient achieved a BMI within the normal range, despite retaining the same glycemic profile notwithstanding the subsequent initiation of insulin pump therapy.

Patient C underwent RYGB surgery for the primary treatment of obesity with a BMI of 47 kg/m² and was only diagnosed with diabetes requiring insulin treatment and positive anti-GAD antibodies 11 years after surgery. This patient experienced a successful
Bariatric surgery in patients with obesity and LADA

We aimed to describe the weight loss response and long-term metabolic outcomes in a small series of patients with LADA undergoing bariatric surgery. All patients had a diagnosis of LADA according to the currently accepted criteria of the American Diabetes Association [16], and were operated on because of weight over 100% ideal body weight, with normal or reduced oral glucose tolerance at the time of surgery.

Overall, the mean preoperative BMI was 40.3 (range 36–47) kg/m², the mean HbA1c was 6.6%, and only 2 patients were under insulin treatment with an average daily dose of 0.68 IU/kg/day. In the last follow-up visit (range: 10–15 years; median: 12 years), BMI had decreased to 24.6 kg/m², and daily insulin requirements for glycemic control were decreased to 0.45 IU/kg in the 2 patients who were under insulin treatment before bariatric surgery (shown in Table 1).

Although the median HbA1c increased significantly after surgery, when values before and after surgery were compared, there were significant improvements in total cholesterol (from 158 mg/dL at surgery to 151 mg/dL at follow-up), HDL cholesterol (from 45 mg/dL at surgery to 58 mg/dL at follow-up), triglycerides (from 94.3 mg/dL at surgery to 59 mg/dL at follow-up), systolic blood pressure (123 mm Hg at surgery to 111 mm Hg at follow-up), and diastolic blood pressure (70 mm Hg at surgery to 66 mm Hg at follow-up). None of the patients developed any complication related to surgery. Two patients do not have any target organ damage nor history suggestive of post-bariatric hypoglycemia; one patient (patient B) experienced difficult metabolic control and several hospitalizations due to severe iatrogenic hypoglycemia and developed diabetic neuropathy and retinopathy.

**Discussion/Conclusion**

In a small series of patients with LADA, bariatric surgery, although failed to demonstrate improved glycemic control, was shown to induce significant weight loss and reduction in daily insulin requirements [22], findings that were corroborated by our own patient series. Grounded on these data, the authors suggest that the main reason for considering bariatric surgery in patients with LADA should be the treatment of obesity and the multitude of its comorbid conditions, instead of targeting glycemic control as primary goal. Patients with LADA experiencing poor glycemic control along with insulin resistance and metabolic syndrome features, which are demonstrated to harbor a higher risk of complications, are probably the best candidates to be considered for bariatric surgery as part of obesity-related diabetes treatment algorithm.

In our small series with a follow-up period of over 10 years, obesity treatment that motivated bariatric surgery was overall accomplished, with significant and sustained weight loss, improved lipid profile, and reduced blood pressure. Moreover, despite the long duration of LADA disease, only one patient developed target organ lesions. Anecdotally, these occurred in the patient who is an active smoker, was diagnosed with LADA at the earliest age of 24 years, and with most difficult glycemic control with recurrent hypoglycemia.

The prevalence of LADA among patients undergoing bariatric surgery may be underestimated. There are several series reporting the outcomes of bariatric surgery in patients with T1D and obesity, while it is unknown which proportion of these patients could meet the criteria for LADA [23–25]. In our series, a patient not previously diagnosed with diabetes at the time of surgery had LADA diagnosed 11 years after the bariatric surgery intervention.

Bariatric surgery can be considered in treatment algorithm of patients with obesity and T2D, with the aim of attaining weight loss and glycemic control. Patients with LADA submitted to bariatric surgery were also demonstrated to achieve successful weight loss, despite not influencing glycemic control nor inducing diabetes remission as often observed for T2D, thus confirming the distinctive natural history of LADA with progressive beta-cell failure [26]. Additionally, weight regain after surgery also influences glycemic control mediated through adipose tissue inflammation [27, 28]. In particular, omental tissue

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**Table 1. Anthropometric and clinical features of subjects with LADA diagnosis before surgery and after surgery**

| Patient | Bariatric surgery type | Follow-up after surgery, years | Age at LADA diagnosis, years | Age at surgery, years | Preoperative BMI, kg/m² | Postoperative BMI, kg/m² | Preoperative HbA1c, % | Postoperative HbA1c, % | Preoperative daily insulin dose, IU/kg/day | Postoperative daily insulin dose, IU/kg/day |
|---------|------------------------|-------------------------------|-----------------------------|----------------------|-------------------------|-------------------------|----------------------|----------------------|------------------------------------------|------------------------------------------|
| A       | RYGB                   | 10                            | 29                          | 38                   | 36                      | 27                      | 7.3                  | 8.0                  | 0.69                                      | 0.58                                      |
| B       | RYGB                   | 12                            | 24                          | 25                   | 38                      | 24                      | 10.4                 | 10.5                 | 0.66                                      | 0.31                                      |
| C       | RYGB                   | 15                            | 53                          | 42                   | 47                      | 23                      | 5.0                  | 9.9                  | NA                                       | 0.50                                      |

HbA1c, hemoglobin A1c; LADA, latent autoimmune diabetes of the adult; RYGB, Roux-en-Y gastric bypass; BMI, body mass index.
inflammation is associated with a decreased in the expres-
sion of lipogenic markers related to glucose intolerance
[29].

Given the pathological differences between T2D and
LADA, some authors suggested that screening for beta-
cell dysfunction should be routinely performed among
bariatric surgery candidates with a prior diagnosis of dia-
betes in order to avoid the disappointment of neutral ef-
fact of the intervention on glycemic control. Furthermore,
some authors have also speculated that LADA, in con-
trast to T2D, should not be an indication for bariatric
surgery.

As a general rule, strict glycemic control is key to im-
prove the overall prognosis of diabetes, including
LADA. Similar to what is observed for patients with
obesity and T2D, bariatric surgery may also facilitate
glycemic control in patients with LADA by reducing
body weight and insulin resistance or even improve in-
sulin secretion as long as the patient still has some pres-
ervation of pancreatic beta-cell function. Bariatric surgi-
cery is currently the most effective short-, medium-, and
long-term treatment for the majority of patients with
obesity and diabetes [30–33]. However, with re-
gard to patients with LADA, data are still very limited
and derived from small series of patients. A recent re-
spective study evaluating the effect of RYGB or of
sleeve gastrectomy in 10 patients with obesity and
LADA did not show any improvement in glycemic con-
tral nor in other cardiometabolic risk factors, despite a
significant body weight reduction [22].

Although a considerable percentage of patients with
obesity develop T2D, this relationship is far from being
linear since even subjects with severe obesity can present
metabolically healthy obesity [34, 35]. Different genetic
backgrounds could account for the variability in the gly-
cemic profile of patients with obesity [36–38].

Excessive weight is a particularly strong risk factor for
LADA in individuals with genetic susceptibility for dia-
betes [7]. This observation suggests that LADA can also
be possibly prevented or delayed through lifestyle modi-
fications. Anti-GAD can be detected in patients with
LADA several years prior to diagnosis, suggesting that in
a similar way as T2D, LADA can have a long pre-diabetes
phase amenable to intervention [39].

The choice of the bariatric surgery technique tai-
lored for these patients may be paramount in modifying
the treatment paradigm of patients with obesity and
LADA. Accumulating evidence suggests that glucose
“variability” with wide glucose fluctuations, particular-
ly if accompanied by frequent hypoglycemic episodes,
Author Contributions Statement

M.G., M.N., and M.P.M. planned and designed the study. M.G. conducted data acquisition. S.S.P., M.G., and M.P.M. participated in analysis and interpretation of data. M.G. and S.S.P. wrote the manuscript; M.N. and M.P.M. revised the manuscript. All the authors approved the submitted version.

References

1. Groop LC, Bottazzo GF, Doniach D. Islet cell antibodies identify latent type I diabetes in patients aged 35–75 years at diagnosis. Diabetes. 1986;35(2):237–41.
2. O’Neil KS, Johnson JL, Panak RL. Recognizing and appropriately treating latent autoimmune diabetes in adults. Diabetes Spectr. 2000;3(9):1326–32.
3. American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care. 2015;38(Suppl 1):S8–16.
4. Naik RG, Palmer JP. Latent autoimmune diabetes in adults (LADA). Rev Endocr Metab Disord. 2003;4(3):233–41.
5. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. Lancet. 2014;383(9922):1084–94.
6. Hjort R, Ahlqvist E, Carlsson PO, Grill V, Groop L, Martinell M, et al. Overweight, obesity and the risk of LADA: results from a Swedish case-control study and the Norwegian HUNT study. Diabetologia. 2018;61(6):1333–43.
7. Hjort R, Löfvenborg JE, Ahlqvist E, Alfredsson L, Andersson T, Grill V, et al. Interaction between overweight and genotypes of HLA, TCF7L2, and FTO in relation to the risk of latent autoimmune diabetes in adults and type 2 diabetes. J Clin Endocrinol Metab. 2019;104(10):4815–26.
8. Lohmann T, Kellner K, Verlohren HJ, Krug J, Steindorf K, Scherbaum WA, et al. Titre and combination of ICA and autoantibodies to glutamic acid decarboxylase discriminate two clinically distinct types of latent autoimmune diabetes in adults (LADA). Diabetologia. 2001;44(8):1005–10.
9. Sabbah E, Savola K, Ebeling T, Kulmala P, Vähäsalo P, Ilonen J, et al. Genetic, autoimmune, and clinical characteristics of childhood- and adult-onset type 1 diabetes. Diabete. 2016;2:249–52.
10. Howson JM, Rosinger S, Smyth DJ, Boehm BO, Group A-ES, Todd JA. Genetic analysis of adult-onset autoimmune diabetes. Diabetol. 2011;60(10):2645–53.
11. Chow A, Switzer NJ, Dang J, Shi X, de Gara C, Birch DW, et al. A systematic review and meta-analysis of outcomes for type 1 diabetes after bariatric surgery. J Obes. 2016;2016:6170719.
12. Wilkin TJ. The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type I as well as type II diabetes. Int J Obes. 2009;33(7):716–26.
13. Pielarski S, Pozzilli P. Latent autoimmune diabetes in adults: a review on clinical implications and management. Diabetes Metab J. 2018;42(6):451–64.
14. Hjort R, Ahlqvist E, Andersson T, Alfredsson L, Carlsson PO, Grill V, et al. Physical activity, genetic susceptibility, and the risk of latent autoimmune diabetes in adults and type 2 diabetes. J Clin Endocrinol Metab. 2020;105(15):e4112–23.
15. Naik RG, Brooks-Worrell BM, Palmer JP. Latent autoimmune diabetes in adults. J Clin Endocrinol Metab. 2009;94(12):4635–44.
16. Olsson L, Grill V, Midithjell K, Alblbaum A, Andersson T, Carlsson S. Mortality in adult-onset autoimmune diabetes is associated with poor glycemic control: results from the HUNT study. Diabetes Care. 2013;36(12):3971–8.
17. Isomaa B, Almgren P, Henrisson M, Taskinen MR, Tuomi T, Groop L, et al. Chronic complications in patients with slowly progressing autoimmune type 1 diabetes (LADA). Diabetes Care. 1999;22(8):1347–53.
18. Wang C, Lu J, Hu W, Yu H, Jiang L, Li M, et al. Evaluating peripheral nerve function in asymptomatic patients with type 2 diabetes or latent autoimmune diabetes of adults (LADA): results from nerve conduction studies (LADA). J Diabetes Complications. 2015;29(2):265–9.
19. Myhll P, Davis WA, Bruce DG, Mackay IR, Zimmet P, Davis TM. Chronic complications and mortality in community-based patients with latent autoimmune diabetes in adults: the fremantle diabetes study. Diabet Med. 2008;25(10):1245–50.
20. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. JAMA. 2006;295(14):1707–8.
21. De Luca M, Angriani L, Himpens J, Busetto L, Scopinaro N, Weiner R, et al. Indications for surgery for obesity and weight-related diseases: position statements from the international federation for the surgery of obesity and metabolic disorders (IFSO). Obes Surg. 2016;26(8):1659–96.
22. Aminian A, Sharma G, Wilson RL, Kashyap SR, Lo Menzo E, Szomstein S, et al. Bariatric surgery in patients with obesity and latent autoimmune diabetes in adults (LADA). Diabetes Care. 2020;43(5):e56–7.
23. Vilarasa N, Rubio MA, Mihambes I, Flores L, Caixàs A, Ciudin A, et al. Long-term outcomes in patients with morbid obesity and type 1 diabetes undergoing bariatric surgery. Obes Surg. 2017;27(4):856–63.
24. Rand H, Weiner RA, Frenken M, Rett K, Weiner S. Obesity and metabolic surgery in type 1 diabetes mellitus. Nutr Hosp. 2013;28 Suppl 2:31–4.
25. Robert M, Belanger P, Hould FS, Marceau S, Tchernev A, Biertho L. Should metabolic surgery be offered in morbidly obese patients with type 1 diabetes? Surg Obes Relat Dis. 2015 Jul–Aug;11(4):798–805.
26. Manning SB, Pucci A, Batterham RL, Finer N. Latent autoimmune diabetes in adults presenting as diabetes “recurrence” after bariatric surgery: a case report. Diabetes Care. 2013;36(8):e120.
27. Catalán V, Gómez-Ambrosi J, Rodríguez A, Pérez-Hernández AL, Gurbindo J, Ramírez B, et al. Activation of noncanonical Wnt signaling through WNT5A in visceral adipose tissue of obese subjects is related to inflammation. J Clin Endocrinol Metab. 2014;99(8):E1407–17.
28. Zatterale F, Longo M, Naderi J, Raciti GA, De Ciderio A, Miele C, et al. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. Front Physiol. 2019;10:1607.
29. Poullain-Godefroy O, Lecoeur C, Pattou F, Frühbeck G, Froguel P. Inflammation is associated with a decrease of lipogenic factors in omental fat in women. Am J Physiol Regul Integr Comp Physiol. 2008;295(1):R1–7.
30. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ. 2013;347:f5934.
31. Yan G, Wang J, Zhang J, Gao K, Zhao Q, Xu X. Long-term outcomes of macrovascular diseases and metabolic indicators of bariatric surgery for severe obesity type 2 diabetes patients with a meta-analysis. PLoS One. 2019;14(12):e0224828.
32. El Khoury L, Chouillard E, Chahine E, Saikaly E, Debs T, Kassis B. Metabolic surgery and diabetes: a systematic review. Obes Surg. 2018;28(7):2069–77.

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33 Courcoulas AP, Goodpaster BH, Eagleton JK, Belle SH, Kalarchian MA, Lang W, et al. Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. JAMA Surg. 2014;149(7):707–15.
34 Chobot A, Górowska-Kowolik K, Sokolowska M, Jarosz-Chobot P. Obesity and diabetes – not only a simple link between two epidemics. Diabetes Metab Res Rev. 2018;34(7):e3042.
35 Blüher M. Metabolically healthy obesity. Endocr Rev. 2020;41(3):405–20.
36 Navarro E, Funtikova AN, Fito M, Schröder H. Can metabolically healthy obesity be explained by diet, genetics, and inflammation? Mol Nutr Food Res. 2015;59(1):75–93.
37 Ramos-Lopez O, Riezu-Boj JJ, Milagro FI, Cuervo M, Goni L, Martínez JA. Genetic and nongenetic factors explaining metabolically healthy and unhealthy phenotypes in participants with excessive adiposity: relevance for personalized nutrition. Ther Adv Endocrinol Metab. 2019;10:2042018819877303.
38 Catalán V, Gómez-Ambrosi J, Rotellar F, Silva C, Rodríguez A, Salvador J, et al. Validation of endogenous control genes in human adipose tissue: relevance to obesity and obesity-associated type 2 diabetes mellitus. Horm Metab Res. 2007;39(7):495–500.
39 Sorgjerd EP, Skorpen F, Kvaloy K, Midthjell K, Grill V. Time dynamics of autoantibodies are coupled to phenotypes and add to the heterogeneity of autoimmune diabetes in adults: the HUNT study, Norway. Diabetologia. 2012;55(5):1310–8.
40 Ceriello A, Ihnat MA. “Glycaemic variability”: a new therapeutic challenge in diabetes and the critical care setting. Diabet Med. 2010;27(8):862–7.