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Surgery for Obesity and Related Diseases 10 (2014) 9–13

SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Relevance of beta-cell function for improved glycemic control after gastric bypass surgery

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Received February 5, 2013; accepted July 27, 2013

Abstract

Background: Residual beta-cell function and gastrointestinal hormones have been suggested as relevant determinants of improved glycemic control ensuing Roux-en-Y gastric bypass (RYGB). The objective of this study was to compare the glycemic control up to 24 months after RYGB in C-peptide negative morbidly obese (MO) type 1 diabetes mellitus (T1 DM) women (n = 7) and C-peptide positive (>.6 ng/mL) MO women with type 2 diabetes mellitus (T2 DM, n = 7) on basal-bolus insulin therapy. The glucagon-like peptide 1 (GLP-1) and glucagon response to a mixed meal challenge were also compared between groups.

Methods: Percent excess weight loss (%EWL), HbA_{1c}, and daily insulin dose (DID) after RYGB were compared between groups. The GLP-1 and glucagon response (area under the curve 0–120 minutes) after a mixed meal at last follow-up visit were also compared.

Results: At 24-months, marked %EWL was observed in women with T1 DM and women with T2 DM (mean ± standard error, 82.6% ± 11.3% and 87.4% ± 30.5%, respectively; $P = .722$]. In women with T1 DM, HbA_{1c} (4 months, $P < .05$) and DID improved transiently ($P < .05$, up to 8 months) but were comparable to baseline thereafter (HbA_{1c}: baseline, 8.3 ± 1.2 and 24 months, 8.2 ± .9, $P = 1.00$; DID: baseline, .61 ± .17 and 24 months .62 ± .12 IU/kg/d, $P = 1.00$]. In contrast, in MO women with T2 DM, HbA_{1c} decreased significantly throughout follow–up, with 2 patients presenting diabetes remission and all but one an $HbA_{1c} < 7\%$ at 24 months. The GLP-1 response was comparable between groups ($P = .612$), and was not accompanied by suppression of the glucagon response to meal intake.

Conclusions: In the absence of residual beta-cell, RYGB results in no significant benefit on glycemic control, despite a marked response of GLP-1 to meal intake. (Surg Obes Relat Dis 2014;10:9–13.)

Keywords: Gastric bypass; Type 1 diabetes mellitus; Type 2 diabetes mellitus; C-peptide; Beta-cell

Residual beta-cell function and gastrointestinal hormones have been suggested as relevant determinants of improved glycemic control ensuing Roux-en-Y gastric bypass (RYGB) [1–3]. It has been proposed that lack of residual beta-cell function, such as in type 1 diabetes mellitus (T1 DM), would result in marginal or no benefit of RYGB on glycemic control [4]. On the other hand, however, it could be hypothesized that even in the absence of residual beta-cell function, such as in patients with T1 DM, RYGB would result in improved glycemic control because of the changes in gastrointestinal hormones occurring after this

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1550-7289/14/$ – see front matter
http://dx.doi.org/10.1016/j.soard.2013.07.020

surgical technique. Specifically, an enlarged glucagon-like peptide 1 (GLP-1) response to meal intake would help improve glycemic control because of its glucagonostatic effects even in the absence of detectable C-peptide [5,6]. Against this background, the primary aim of our study was to compare the glycemic control up to 24 months after RYGB in 2 groups of patients with differing residual beta–cell function before surgery: morbidly obese women with long-standing, C-peptide negative (<.1 ng/mL) T1 DM and morbidly obese women with C-peptide positive (>.6 ng/mL) type 2 diabetes mellitus (T2 DM). As secondary aim, we compared the GLP-1 and glucagon response with a meal challenge in the 2 study groups.

Methods

A retrospective analysis of prospectively collected data in 2 groups of patients (n = 7 per group) who underwent RYGB [2] at our institution between July 2005 and October 2011 was performed. Diagnosis of T1 DM was based on medical history, insulin use since diagnosis, positivity of glutamic acid decarboxylase antibodies (GAD-Ab) and islet cell autoantibodies at the time of diagnosis, and a fasting C-peptide <.1 ng/mL before surgery. Before surgery, all T1 DM patients were on basal-bolus insulin regime. Women in the T2 DM group were selected among a series of T2 DM patients who underwent RYGB at our institution in the same time period [2]. Inclusion criteria for women in the T2 DM group included glutamic acid decarboxylase antibody negativity, being on a basal-bolus insulin regime, and the presence of a fasting C-peptide >.6 ng/mL. The 2 groups were matched for DM duration, and HbA_{1c} before surgery. Body mass index (BMI, weight [kg]/height [$m^{2]}$), percent excess weight loss (%EWL), HbA_{1c} (%), and daily insulin dose (IU/kg/d) were prospectively collected before surgery and at 4, 8, 12, and 24 months thereafter [2]. The study was approved by the Hospital Ethics Committee and written informed consent was obtained from all participants.

Fasting plasma C-peptide was measured by radioimmunoassay (RIA) (Millipore Corporation, Billerica, MA), the lowest limit of detection being .1 ng/mL. The GLP-1 and glucagon response after a mixed-liquid meal challenge was assessed at last follow up visit as previously described [7]. In brief, patients attended the research facility after an overnight fasting. A canula was inserted in the distal forearm for venous sample collection. After withdrawal of fasting samples, patients consumed a 250-mL standardized mixed liquid meal (Isosource Energy, Novartis, Switzerland) containing 398 kcal, with 50% calories as carbohydrates, 15% as protein, and 35% as fat. Blood was drawn at 30, 60, 90, and 120 minutes after meal ingestion. Samples were collected on ice into EDTA tubes containing aprotinin at a final concentration of 500 kIU/mL of blood and were immediately processed, to avoid the breakdown of peptides. After a centrifugation at 4ºC, plasma samples were kept frozen at –80ºC until analysis. Human plasma total GLP-1 and glucagon were measured with commercially available RIA (GLP-1 [total] RIA kit and glucagon RIA kit; Linco Research, Inc., St Charles, MO]. Limits of sensitivity for the GLP-1 and glucagon are 3 pM and 20 pg/mL, respectively. The intraassay and interassay coefficients of variation of the GLP-1 and glucagon assay were <20% and <9%, respectively.

Data are expressed as mean (standard deviation) unless specified otherwise. Normality of study variables was assessed with the Kolmogorov-Smirnov normality test. All variables followed Gaussian distribution (P value >.05); consequently, parametric test were used in statistical analysis. Effect of surgery on glycated hemoglobin, BMI, weight loss, and daily insulin dose during follow-up were compared among groups using two-way repeated measures ANOVA. Clinical features at baseline and during follow-up and parameters obtained during mixed meal test were compared between groups using t test or χ^2 test as appropriate. Changes in study variables within group throughout follow-up were evaluated using repeated measures ANOVA. Statistical significance was set at a P value <.05. The AUC for GLP-1 and glucagon was calculated using the trapezoidal method. Statistical analysis was performed using SPSS 17.0 (Chicago, IL), with statistical significance set at $P < .05$.

Results

Baseline and follow up data are shown in Table 1. At baseline, women with T1 DM were younger (T1 DM: 38.2 ± 13.3 years versus T2 DM 57.0 ± 6.4 years; $P = .005$], and presented a lower BMI ($P = .010$) compared with women with T2 DM. Diabetes duration was not significantly different between groups ($P = .675$), and ranged 5.5 to 22.0 years. Likewise, at baseline daily insulin dose ($P = .160$) and HbA_{1c} ($P = .149$) were comparable between groups. All study patients except one T1 DM participant presented an HbA_{1c} >7.0% before RYGB. Before surgery, 2 of the 7 women with T1 DM presented nonproliferative diabetic retinopathy, and none presented other microvascular complications. In the T2 DM group, 4 of 7 women presented diabetic retinopathy (3 with proliferative and 1 with nonproliferative diabetic retinopathy), and 1 of 7 women showed positive microalbuminuria at presurgical evaluation. None of the participants with T1 DM referred previous history of macrovascular disease. In contrast, 2 of 7 women with T2 DM in our cohort presented positive history of macrovascular disease. In the T2 DM group, presurgical fasting C-peptide was 1.5 ± .9 ng/mL.

As shown in Table 1, surgery was associated with significant ($P < .001$) and comparable %EWL and BMI change ($P = .274$ and $P = .476$, respectively) in the 2 study groups. A significantly larger BMI was recorded in the T2