Bariatric Surgery Reduces Oxidative Stress by Blunting 24-h Acute Glucose Fluctuations in Type 2 Diabetic Obese Patients

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OBJECTIVE — We evaluated the efficacy of malabsorptive bariatric surgery on daily blood glucose fluctuations and oxidative stress in type 2 diabetic obese patients.

RESEARCH DESIGN AND METHODS — The 48-h continuous subcutaneous glucose monitoring was assessed in type 2 diabetic patients before and 1 month after biliopancreatic diversion (BPD) ($n = 36$), or after diet-induced equivalent weight loss ($n = 20$). The mean amplitude of glycemic excursions and oxidative stress (nitrotyrosine) were evaluated during continuous subcutaneous glucose monitoring. During a standardized meal, glucagon-like peptide (GLP)-1, glucagon, and insulin were measured.

RESULTS — Fasting and postprandial glucose decreased equally in surgical and diet groups. A marked increase in GLP-1 occurred during the interprandial period in surgical patients toward the diet group ($P < 0.01$). Glucagon was more suppressed during the interprandial period in surgical patients compared with the diet group ($P < 0.01$). Mean amplitude of glycemic excursions and nitrotyrosine levels decreased more after BPD than after diet ($P < 0.01$).

CONCLUSIONS — Oxidative stress reduction after biliopancreatic diversion seems to be related to the regulation of glucose fluctuations resulting from intestinal bypass.

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Cogent evidence suggests that acute fluctuations of glucose around a mean value over a daily period of intermittent hyperglycemia and obesity, activating oxidative stress, might play an important role in cardiovascular disease in type 2 diabetic patients (1–3). As a consequence, it is strongly suggested that a global antidiabetic strategy should be aimed at reducing the different components of dysglycemia (A1C, fasting and postprandial glucose, and glucose variability). Although improvements in glycemic control have been observed in subjects with type 2 diabetes after malabsorptive bariatric surgery (4), there are no studies that have examined the surgery effects on the glucose fluctuations over a daily period and on oxidative stress production. Because the regulation strategy of daily glucose fluctuations attempts to normalize incretin secretions over a daily period (5), this study was conducted to evaluate the efficacy of biliopancreatic diversion (BPD), as malabsorptive bariatric surgery, on glucagon-like peptide (GLP)-1 and glucagon as well as on oxidative stress activation (nitrotyrosine) and daily blood glucose fluctuations during continuous subcutaneous glucose monitoring in type 2 diabetic obese patients.

RESEARCH DESIGN AND METHODS

— A total of 56 obese type 2 diabetic patients (BMI >40 kg/m^2), eligible candidates for BPD, not on insulin, exenatide, or dipeptidyl peptidase 4 inhibitors, were studied. All participants signed an informed consent, approved by our institution. One group was studied before and 1 month after GBP (surgical group, $n = 36$). A second group, fulfilling the same recruitment criteria, was studied before and after a 10-kg diet-induced weight loss (diet group, $n = 20$). All participants have voluntarily chosen to undergo to surgery or dietary intervention. In the diet group, the mean recommended daily caloric intake was 1,100 kcal (from 1,050 to 1,250 kcal). The recommended dietary regimen was 55% carbohydrates, 30% lipid, and 15% protein, and this regimen was followed on an outpatient basis until 10-kg weight loss. The surgical group had undergone BPD that was performed as previously described (6). All patients received the same parenteral nutrition regimen (1,400 kcal/day) during the first 6 days after surgery; then the same daily caloric intake of the diet group was recommended. Continuous subcutaneous glucose monitoring measurements (Glucoday, Menarini, Italy) were monitored, over a period of 3 consecutive days, at baseline and within 1 month after surgery in the surgical group and after a 10-kg diet-induced weight loss in the diet group. The mean amplitude of glycemic excursions (MAGE), which has been described by Service et al. (7), was used for assessing glucose fluctuations during the fasting plasma glucose (FPG), postprandial plasma glucose (PPG), diurnal and nocturnal interprandial periods on study days 1 and 2. Standardized meal tests with 24-h sampling comprising three mixed meals were performed on days 1, 2, and 3 (breakfast: 310 kcal; lunch: 440 kcal; dinner: 350 kcal). During the standardized meal, glucose, GLP-1 (enzyme-linked immunosorbent assay [ELISA], D.B.A., Santa Cruz Biotechnology, Milan, Italy), glucagon

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Table 1—*Clinical characteristics and metabolic profile before and after 1 month after biliopancreatic diversion or 10-kg weight loss*

	Biliopancreatic diversion group			Diet group		
	Baseline	After 1 month	*P*	Baseline	After 10-kg weight loss	*P*
Age (years)	45 ± 8	—	—	46 ± 6	—	—
Male/female sex (*n*)	16/20	16/20	—	9/11	9/11	—
BMI (kg/m^2)	43.7 ± 2.9	39.1 ± 3.2	0.01	43.6 ± 3.1	38.9 ± 3.3	0.01
Systolic blood pressure (mmHg)	120 ± 12	119 ± 13	NS	121 ± 13	120 ± 10	NS
Diastolic blood pressure (mmHg)	79 ± 5	78 ± 3	NS	80 ± 4	79 ± 3	NS
Diabetes duration (years)	3.2 ± 4	—	—	3.1 ± 6	—	—
Risk factors						
Hypertension	9 (25)	—	—	5 (25)	—	—
Hypercholesterolemia	4 (11)	—	—	2 (10)	—	—
Smokers	4 (11)	—	—	2 (10)	—	—
Laboratory						
Fasting glycemia (mg/dl)	129 ± 19	109 ± 12	0.01	128 ± 13	106 ± 14	0.01
2-h postprandial glycemia (mg/dl)	186 ± 23	164 ± 16	0.01	185 ± 21	165 ± 15	0.01
A1C (%)	7.1 ± 0.4	6.8 ± 0.3	0.01	7.0 ± 0.5	6.6 ± 0.4	0.01
MAGE (mg/dl glucose)	61 ± 13	35 ± 12*	0.01	60 ± 21	55 ± 14	NS
Nitrotyrosine (μmol/l)	0.81 ± 0.04	0.44 ± 0.03*	0.01	0.79 ± 0.03	0.76 ± 0.06	NS
Fasting insulin (pmol/l)	170 ± 55	131 ± 48	0.01	178 ± 68	127 ± 50	0.01
Postmeal insulin AUC (pmol/l)	498 ± 179	669 ± 135	0.01	505 ± 157	655 ± 122	0.01
Interprandial insulin AUC (pmol · l^{-1} · min^{-1})	325 ± 124	290 ± 108	0.01	339 ± 111	301 ± 122	0.01
Fasting glucagon (ng/l)	71.9 ± 12	65.3 ± 11.6	NS	69.9 ± 13	66.2 ± 11	NS
Postmeal glucagon AUC (ng/l)	68.3 ± 14	50 ± 9	0.01	66.7 ± 10	53 ± 12	0.01
Interprandial glucagon AUC (ng · l^{-1} · min^{-1})	70.7 ± 13	53.6 ± 12*	0.01	69.3 ± 12	68.6 ± 13	NS
Fasting GLP-1 (pmol/l)	6.5 ± 1.2	7.1 ± 1.1	NS	6.6 ± 1.8	6.9 ± 1.5	NS
Postmeal GLP-1 AUC (pmol/l)	9.9 ± 2.1	18.7 ± 3.2	0.01	10.2 ± 2.9	19.3 ± 2.6	0.01
Interprandial GLP-1 AUC (pmol · l^{-1} · min^{-1})	6.2 ± 1.1	11.7 ± 2.5*	0.01	6.5 ± 1.3	7.2 ± 1.4	NS
Active therapy						
ACE inhibitors	5 (14)	5 (14)	—	3 (15)	3 (15)	—
Angiotensin II antagonists	4 (11)	4 (11)	—	2 (10)	2 (10)	—
Diuretics	4 (11)	4 (11)	—	2 (10)	2 (10)	—
Aspirin	10 (28)	10 (28)	—	6 (30)	6 (30)	—
Statins	8 (22)	8 (22)	—	5 (25)	5 (25)	—
Metformin	32 (89)	32 (89)	—	18 (90)	18 (90)	—
Thiazolinediones	10 (28)	10 (28)	—	6 (30)	6 (30)	—

Data are means ± SD or *n* (%) unless otherwise indicated. Postmeal (0–120 min) and interprandial (120–300 min after meal) areas under the curve (AUCs) for outcome variables were calculated using the trapezoidal method. *$P < 0.05$ compared with the diet group. Nitrotyrosine was assayed as described previously (8): the standard curve was constructed with serial dilution of a nitrated protein solution; the limit of detection of the assay was 10 nmol/l, with intra- and interassay coefficients of variation of 4.5 and 8%, respectively.

(ELISA, D.B.A., Santa Cruz Biotechnology), and insulin (Ares, Serono, Italy) were evaluated at the following times: 0, 60, 120, 180, 240, and 300 min, with the meal beginning immediately after time 0 and consumed within 15 min. Nitrotyrosine (anti-nitrotyrosine rabbit polyclonal antibody; D.B.A., Santa Cruz Biotechnology) (8) was assessed at baseline and after 1 month in the surgical group and after a 10-kg diet-induced weight loss in the diet group. A *P* value <0.05 defined as statistical significance. Simple Pearson correlation was used to assess linear relationships between single variables.

RESULTS — At baseline, patients were matched for anthropometric, physical activity, metabolic, and hormonal variables (Table 1) . Duration of weight loss was shorter for the surgical group (30.2 ± 11.9 days) than the diet group (60.2 ± 10.1 days; $P < 0.001$). BMI, A1C, FPG, and PPG decreased significantly and equally in surgical and diet groups (Table 1). Despite similar data in A1C, FPG, and PPG during weight loss in the surgical and diet groups, pattern of daily glucose fluctuations (MAGE) improved after BPD ($P < 0.01$), but not in the diet group, despite a similar weight loss (Table 1). Focusing on hormone profiles during a standard meal and interprandial periods, one can highlight that increase in GLP-1 after food intake was substantially identical in the two groups, whereas a significant ($P < 0.05$) and sustained increase during the interprandial period (from 120 to 300 min after a meal) of active GLP-1 in

BPD toward diet patients occurred (Table 1). In addition, plasma glucagon levels were more suppressed during the interprandial period in surgical patients compared with diet patients (Table 1), but such differences did not reach statistical significance during the postprandial period. Finally, both fasting and postmeal plasma insulin level changes were similar in the two groups (Table 1). Nitrotyrosine levels were significantly lower after BPD compared with diet ($P < 0.01$) (Table 1). Interestingly enough, nitrotyrosine reductions were directly related to MAGE changes in the surgery group ($r = 0.55$, $P < 0.01$). Moreover, MAGE changes were directly related to interprandial GLP-1 increases ($r = 0.45$, $P < 0.01$). Finally, the GLP-1 changes were inversely correlated with the glucagon changes ($r = -0.42$, $P < 0.01$) and directly correlated with insulin changes ($r = 0.52$, $P < 0.01$).

CONCLUSIONS — BPD, when performed in obese diabetic patients, is effective in improving glycemic control (6). In this study, the efficacy of BPD on A1C, FPG, and PPG reductions was comparable to the diet intervention. Nevertheless, our study shows evidence that the effects of BPD on daily glucose fluctuations, as estimated from MAGE indexes that reflect both upward and downward glucose changes, were more pronounced in the BPD group than in the diet group, which could be due to different effects on incretin secretion. Although the well-matched surgical and diet groups lost the same amount of weight, their changes in incretin levels were strikingly different. According to the previous data (9,10), both GLP-1 and glucagon responses to standardized meals markedly increased 1 month after BPD and 10-kg diet-induced weight loss, without significant differences among the groups. However, BPD patients showed a significantly better daily GLP-1 and glucagon profiles in interprandial periods, which could be responsible for a MAGE within a shorter range. From a more practical point of view, since BPD, by blunting the daily fluctuations of glucose, is associated with a reduction of oxidative stress, the malabsorptive surgery may have an important role not only in the normalization of glycemic variability but also in reducing the impact of diabetes in vascular health.

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