

Bariatric surgery reduces oxidative stress by blunting 24-hours acute glucose fluctuations in type 2 diabetic obese patients

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Running head: Daily glucose fluctuations and bariatric surgery

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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-48-h continuous subcutaneous glucose monitoring (CSGM) were assessed in type 2 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 (MAGE) and oxidative stress (nitrotyrosine) were evaluated during CSGM. During a standardized meal, glucagon-like peptide-1 (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 interprandial period in surgical patients toward diet group ($P<0.01$). Glucagon was more suppressed during interprandial period in surgical patients compared to diet group ($P<0.01$). MAGE and nitrotyrosine levels decreased more after GBP than after diet ($P<0.01$).

Conclusions Oxidative stress reduction after BPD seem to be related to the regulation of glucose fluctuations resulting from intestinal bypass.

Coherent evidence suggests that acute fluctuations of glucose around a mean value over a daily period intermittent hyperglycemia and obesity, activating the oxidative stress, might play an important role on cardiovascular diseases of type 2 diabetic patients (1,2,3). As a consequence, it is strongly suggested that a global antidiabetic strategy should be aimed at reducing to a minimum the different components of dysglycemia (HbA1c, fasting and postprandial glucose, and glucose variability). Although improvements in glycemic control have been observed in subjects with type 2 diabetes following 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 GLP-1 and glucagon as well as on oxidative stress activation (nitrotyrosine) and daily blood glucose fluctuations during CSGM in type 2 diabetic obese patients.

RESEARCH DESIGN AND METHODS

Fifty-six obese type 2 diabetic patients (BMI >40 kg/m²) eligible candidates for BPD, not on insulin, exenatide, or DPP-IV 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 composition

of dietary regimen was 55% carbohydrates, 30% lipid and 15% protein, and were followed on an outpatient basis until 10-kg weight loss. The surgical-group has undergone to BPD that was performed as previously described (6). All patients received the same parenteral nutrition regimen (1400 kcal/day) during the first 6 days after surgery; then the same daily caloric intake of diet group was recommended. CSGM measurements (Glucoday, Menarini-Italy) were monitored, over a period of 3 consecutive days, at baseline and within 1 month after surgery in surgical-group and after 10-kg diet-induced weight loss in diet-group. The MAGE, which has been described by Service et al (7), was used for assessing glucose fluctuations during the fasting (FPG), postprandial (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 (ELISA, D.B.A., Italy), glucagon (ELISA, D.B.A., Italy), and insulin (Ares, Serono, Italy) were evaluated at the following times: 0-60-120-180-240-300 min, with the meal beginning immediately after the Time 0 and consumed within 15 min. Nitrotyrosine (anti-nitrotyrosine rabbit polyclonal antibody, DBA-Milan) (8) was assessed at baseline and after 1 month in the surgical-group and after 10-kg diet-induced weight loss in 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). Duration of weight loss was shorter for the surgical-group

(30.2 ± 11.9 d) compared to diet-group (60.2 ± 10.1 d; $P < 0.001$). BMI, HbA1c, FPG and PPG decreased significantly and equally in the surgical and diet groups (Table). Despite similar data in HbA1c, FPG and PPG during weight loss in surgical and diet groups, pattern of daily glucose fluctuations (MAGE) improved after BPD ($P < 0.01$), but not in diet group despite a similar weight loss (Table). Focusing on hormone profiles during 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 interprandial period (from 120 to 300 min after meal) of active GLP-1 in BPD toward diet patients occurred (Table). In addition, plasma glucagon levels were more suppressed during interprandial period in surgically patients compared to diet patients (Table), but such differences did not reach statistical significance during the postprandial period. Finally, both fasting and postmeal plasma insulin levels changes were similar in the two groups (Table). Nitrotyrosine levels were significantly lower after BPD compared with diet ($P < 0.01$) (Table). Interestingly enough, nitrotyrosine reductions were directly related to MAGE changes in 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 are effective at improving glycemic control (6). In this study, the efficacy of BPD on HbA1c, FPG and PPG reductions was comparable to the diet intervention. Nevertheless, our study evidence 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 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, are 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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Table. Clinical characteristics and metabolic profile before and after 1 months after biliopancreatic diversion or 10-kg weight loss

Variables	Bilio pancreatic Diversion group			Diet group		
	Baseline	After 1 months	P	Baseline	After 10-kg weight loss	P
Age, y	45±8	/	/	46±6	/	/
Male/Female gender, n	16/20	16/20	/	9/11	9/11	/
Body mass index, 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, yrs	3.2±4	/	/	3.1±6	/	/
Risk factors						
Hypertension, n (%)	9 (25)	/	/	5 (25)	/	/
Hypercholesterolemia, n (%)	4 (11)	/	/	2 (10)	/	/
Smokers, n (%)	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
HbA1c (%)	7.1±0.4	6.8±0.3	0.01	7.0±0.5	6.6±0.4	0.01
MAGE, mg/dl of 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, n (%)	5 (14)	5 (14)	/	3 (15)	3 (15)	/
AT ₂ antagonists, n (%)	4 (11)	4 (11)	/	2 (10)	2 (10)	/
Diuretics, n (%)	4 (11)	4 (11)	/	2 (10)	2 (10)	/
Aspirin, n (%)	10 (28)	10 (28)	/	6 (30)	6 (30)	/
Statins, n (%)	8 (22)	8 (22)	/	5 (25)	5 (25)	/
Metformin, n (%)	32 (89)	32 (89)	/	18 (90)	18 (90)	/
Thiazolidinediones, n (%)	10 (28)	10 (28)	/	6 (30)	6 (30)	/

GLP-1, glucagon-like peptide-1. Postmeal (0-120 min) and interprandial (120–300 min after meal) AUCs for outcome variables were calculated using the trapezoidal method. Data are as means ± SD. *P < 0.05 compared to diet-group. Nitrotyrosine was assayed according to Ter Steege et al. (7): 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 coefficient of variations of 4.5% and 8%, respectively.