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GLP-1 and Glucose Tolerance After Sleeve Gastrectomy in Morbidly Obese Subjects With Type 2 Diabetes

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Although GLP-1 has been suggested as a major factor for the marked improvement of glucose tolerance commonly seen after sleeve gastrectomy (SG), several observations challenge this hypothesis. To better understand the role of GLP-1 in the remission of type 2 diabetes mellitus (T2DM) long term after SG in humans, we conducted two separate cross-sectional studies: *1*) the GLP-1 response to a standardized mixed liquid meal (SMLM) was compared in subjects with T2DM antedating SG but with different long-term (>2 years) T2DM outcomes (remission, relapse, or lack of remission) (study 1) and *2*) the effect of GLP-1 receptor blockade with exendin (9-39) on glucose tolerance was examined in subjects with T2DM antedating surgery, who had undergone SG and presented with long-term T2DM remission (study 2). In study 1, we observed a comparable GLP-1 response to the SMLM regardless of the post-SG outcome of T2DM. In study 2, the blockade of GLP-1 action resulted in impaired insulin secretion but limited deterioration of glucose tolerance. Thus, our data suggest the enhanced GLP-1 secretion observed long term after SG is neither sufficient nor critical to maintain normal glucose tolerance in subjects with T2DM antedating the surgery.

GLP-1 has been suggested as a critical mediator for the marked improvement of glucose tolerance in subjects with type 2 diabetes mellitus (T2DM) commonly seen after Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) (1). However, this view has been challenged by *1*) studies in humans—performed long after RYGB using the GLP-1 receptor antagonist exendin (9-39) (Ex 9-39)—showing that blockade of GLP-1 action results in marked decrease in insulin secretion but limited impact on glucose tolerance (2,3); *2*) data showing the GLP-1 response to meal stimuli does not differ between T2DM patients who after RYGB presented with lack of remission, partial remission, or relapse of T2DM (4); and *3*) mouse data demonstrating that whole-body GLP-1 receptor deficiency does not influence the glycemic response to SG (5).

To gain further insight into the role of GLP-1 in the remission of T2DM long term after SG in humans, We conducted two separate cross-sectional studies: *1*) we compared the GLP-1 response to a standardized mixed liquid meal (SMLM) in subjects with T2DM antedating SG but with different long-term (>2 years) T2DM outcomes (remission, relapse, or lack of remission) (study 1) and *2*) we examined the effect of GLP-1 receptor blockade with Ex 9-39 on glucose tolerance in subjects with T2DM antedating surgery, who had undergone SG and presented with long-term T2DM remission (study 2).

RESEARCH DESIGN AND METHODS

Participants in study 1 (n = 23) were selected out of our series of T2DM patients who had undergone SG at least 2 years before study entry (n = 55), of whom 18 (33%), 31 (56%), and 6 (11%) presented with nonremission, remission, or relapse of T2DM, respectively (6,7). All subjects

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in the relapse group and 10 and 7 subjects from the remission and nonremission group with similar sex distribution, presurgical BMI, and length of follow-up volunteered to participate. The GLP-1, glucose, C-peptide, and glucagon response to a SMLM (398 kcal, 50% carbohydrate, 35% from fat, 15% protein, Isosource Energy; Novartis, Switzerland) challenge were assessed as previously reported (4).

Study 2 was a case-control study involving three groups of subjects: *1*) individuals who had undergone SG ≥24 months before inclusion in the study, had pharmacologically treated T2DM prior to surgery with duration of >6 months, and presented T2DM remission at the time of evaluation (SG-DMR group; n = 8); *2*) nondiabetic individuals who underwent SG ≥24 months prior to the study (SG-control group; n = 6); and *3*) normal-weight, nonoperated, healthy subjects (NO-control group; n = 8). The three groups were matched for age and sex distribution. The SG-DMR and SG-control groups were also matched by BMI and length of post-surgical follow-up. Sample size was calculated to detect differences among groups with a statistical power of 80% and an α error of 0.05 based on our previously published observation of a 10% increase in the area under the curve of plasma glucose ($AUC_{0–120}$) during Ex 9-39 versus saline infusion in control subjects (2) and based on the expectation of at least a 30% increase in the $AUC_{0–120}$ with Ex 9-39 versus saline infusion in the SG-DMR group. The assessment of plasma glucose, insulin, C-peptide, GLP-1, and gastric inhibitory polypeptide (GIP) to an SMLM, during Ex 9-39 (Clinalfa Basic; Bachem, Weil am Rhein, Germany) or saline infusion was performed as previously described (2).

In both studies, β-cell function parameters were derived from mathematical modeling of plasma glucose and C-peptide concentrations measured during SMLM, as previously described (8). Insulin sensitivity was estimated either from fasting plasma insulin and glucose measurements (homeostasis model assessment of insulin resistance) or from glucose and C-peptide plasma concentrations throughout the SMLM, as described by Matsuda and DeFronzo (9), using C-peptide instead of insulin as proposed by Radaelli et al. (10). AUC was calculated using the trapezoidal method.

Both studies received approval by the hospital ethics committee. Written informed consent from all participants was obtained.

Table 1—Clinical and biochemical characteristics and glucose and hormonal responses to a SMLM in participants in study 1 according to glucose tolerance at the time of evaluation

	Remission	Relapse	Nonremission	*P*
n	10	6	7	
Age (years)	50.9 ± 10.6	59.4 ± 13.6	58.7 ± 5.5	0.199
Sex (female/male)	7/3	4/2	4/3	0.500
Presurgery BMI (kg/m^2)	46.1 ± 5.0	44.9 ± 5.3	43.1 ± 7.2	0.588
T2DM duration (years)	3.8 ± 2.1	5.2 ± 1.9	12.0 ± 6.0*,[a]	0.002
Presurgery HbA_{1c} [% (mmol/mol)]	6.8 ± 1.2 (51 ± 13.1)	6.9 ± 1.9 (52 ± 20.8)	9.4 ± 1.9*,[a] (79 ± 20.8)	0.010
Presurgery insulin treatment (%)	0	17	100*,[a]	<0.001
BMI at evaluation (kg/m^2)	32.7 ± 3.0	37.5 ± 7.4	32.4 ± 4.7	0.149
EWL at evaluation (%)	63 ± 15	42 ± 27	62 ± 11	0.069
HbA_{1c} at evaluation [% (mmol/mol)]	5.1 ± 0.3 (32 ± 3.3)	6.4 ± 0.2* (46 ± 2.2)	7.7 ± 0.8*,[a] (61 ± 8.7)	<0.001
Follow-up period (years)	3.0 ± 1.0	3.9 ± 1.3	3.2 ± 0.8	0.216
Fasting glucose (mg/dL)	90 ± 8	140 ± 42	222 ± 79*,[a]	<0.001
2-h plasma glucose (mg/dL)	106 ± 21	186 ± 33*	350 ± 92*,[a]	<0.001
$AUC_{0–120}$ glucose (mg · dL^{-1} ·min)	16,719 ± 2,030	27,487 ± 7,304*	40,476 ± 10,789*,[a]	<0.001
$AUC_{0–120}$ C-peptide (nmol · L^{-1} · min)	312 ± 47	289 ± 85	190 ± 92*,[a]	0.009
Total insulin output (nmol · m^{-2})	49 ± 8	40 ± 13	28 ± 13*	0.004
β-Cell glucose sensitivity (pmol · min^{-1} · m^{-2} · mmol/L^{-1})	86 ± 39	38 ± 22*	16 ± 8*	<0.001
Rate sensitivity (nmol · m^{-2} · mmol/L)	1.64 ± 1.23	0.48 ± 0.60*	0.42 ± 0.19*	0.016
Potentiation factor	1.29 ± 0.34	1.31 ± 0.46	0.83 ± 0.20*,[a]	0.022
IS (mL · min^{-1} · m^{-2})	3.5 ± 1.0	2.1 ± 1.2	2.6 ± 1.9	0.149
$AUC_{0–120}$ glucagon (pg · dL^{-1} · min · 10^3)	8.8 ± 2.5	14.1 ± 5.6*	13.1 ± 2.5	0.014
$AUC_{0–120}$ GLP-1 (pmol · L^{-1} · min · 10^3)	4.56 ± 2.83	4.95 ± 1.78	5.06 ± 1.37	0.900

Data are means ± SD. EWL, excess of weight loss; IS, insulin sensitivity. *P < 0.05 compared with remission group. [a]P < 0.05 compared with relapse group.

Data are expressed as mean (SD) unless otherwise specified. Parametric tests were used in statistical analysis, as all variables followed Gaussian distribution (Kolmogorov-Smirnov test, $P > 0.05$). Paired *t* test was used for within-group comparisons in studies with Ex 9-39 or saline. Group comparisons in study 1 and study 2 were performed using ANOVA with post hoc analysis. In study 2, parameters obtained during Ex 9-39 or saline infusions were compared among groups using two-way ANOVA for repeated measures. Statistical analysis was performed using SPSS 17.0. Statistical significance was set at $P < 0.05$.

RESULTS

Study 1

As shown in Table 1 and Supplementary Fig. 1, the glucose response to the SMLM challenge differed among groups ($P < 0.001$). In addition, β-cell glucose and rate sensitivity were impaired in relapsing and nonremitting patients—to a larger extent in the latter in whom total insulin output and potentiation were also lower than in the remission group. Of note, no differences were found among the three groups in the GLP-1 $AUC_{0–120}$ or the GLP-1 concentrations during the test. In contrast, the glucagon response was significantly enhanced in relapsing and nonremitting patients alike compared with patients who were in remission.

Study 2

The clinical features of participants in study 2 are shown in Table 2. Time since surgery ranged from 2.0 to 5.2 years. As shown in Fig. 1 and Table 3, patients in the SG-control group had slightly lower fasting glucose levels than the SG-DMR ($P = 0.013$) or NO-control group. Ex 9-39 infusion was associated with a significant increase in fasting glucose, similarly in the three groups. Meal ingestion gave rise to similar peak and 2-h glucose levels in the three groups. GLP-1 blockade was associated with higher and earlier glucose peak, higher 2-h glucose, higher mean glucose, and greater glucose $AUC_{0–120}$, with no differences in the magnitude of the effect across groups. This was also true of the incremental glucose AUCs during the meal. Fasting insulin levels did not differ across groups and were not influenced by Ex 9-39. As expected from their higher glucose levels, individuals in the SG-DMR group presented with higher fasting insulin secretion rates than the SG-control group; however, Ex 9-39 had no effect on this parameter. Total insulin output did not differ among groups prior to Ex 9-39 infusion, but Ex 9-39 was associated with a blunted insulin response in both SG groups compared with the NO-control group ($P_{interaction} = 0.040$). In the SG-DMR group, Ex 9-39 resulted in decreased β-cell glucose sensitivity ($P = 0.013$) but no significant change in the potentiation factor or rate sensitivity.

Prior to meal ingestion, Ex 9-39 had no effect on glucagon or GIP plasma concentrations but was associated with a significant increase in GLP-1 in the three groups ($P < 0.001$) with no treatment-group interaction ($P = 0.793$) (Supplementary Table 1 and Supplementary Fig. 2). As expected, meal ingestion per se elicited a higher GLP-1 response in the two surgical groups compared with the NO-control group ($P = 0.015$), which was not coupled to a suppression of the glucagon response (Supplementary Fig. 2). Ex 9-39 was associated with a further increase in the GLP-1 response in all groups ($P < 0.001$), which was associated with increases in the glucagon response.

DISCUSSION

Our data show that *1*) the striking GLP-1 response to meal intake observed long term after SG is not sufficient to maintain normal glucose tolerance in subjects with T2DM antedating the surgery and *2*) that in subjects with surgically induced long-term T2DM remission, blockade of GLP-1 action results in limited deterioration of glucose tolerance. Thus, our results strongly suggest

Table 2—Clinical features of participants in study 2

	NO-control group	SG-control group	SG-DMR group	*P*
n	8	6	8	
Age (years)	50.0 ± 13.0	52.1 ± 13.1	49.8 ± 12.4	0.936
Sex (female/male)	6/2	4/2	6/2	0.926
Presurgery BMI (kg/m^2)	—	44.9 ± 5.3	47.7 ± 5.5	0.506
T2DM duration (years)	—	—	2.8 ± 1.8	
Presurgery HbA_{1c} [% (mmol/mol)]	—	5.0 ± 0.3 (31 ± 3.3)	7.1 ± 2.1 (54 ± 23.0)	0.025
BMI at evaluation (kg/m^2)	23.3 ± 2.0	31.1 ± 4.2*	32.7 ± 2.3*	<0.001
EWL at evaluation (%)	—	75 ± 19	64 ± 16	0.265
Fasting plasma glucose (mg/dL)	88 ± 7	81 ± 11	91 ± 8	0.086
HbA_{1c} at evaluation [% (mmol/mol)]	5.5 ± 0.3 (37 ± 3.3)	5.4 ± 0.4 (36 ± 4.4)	5.3 ± 0.2 (34 ± 2.2)	0.369
HOMA-IR	1.3 ± 0.8	1.4 ± 0.8	2.4 ± 0.6	0.021
Time of postsurgical follow-up (years)	—	2.9 ± 0.9	3.4 ± 0.9	0.433

Data are expressed as means ± SD. EWL, excess of weight loss; HOMA-IR, homeostasis model assessment of insulin resistance. *$P <$ 0.05 compared with NO-control group.

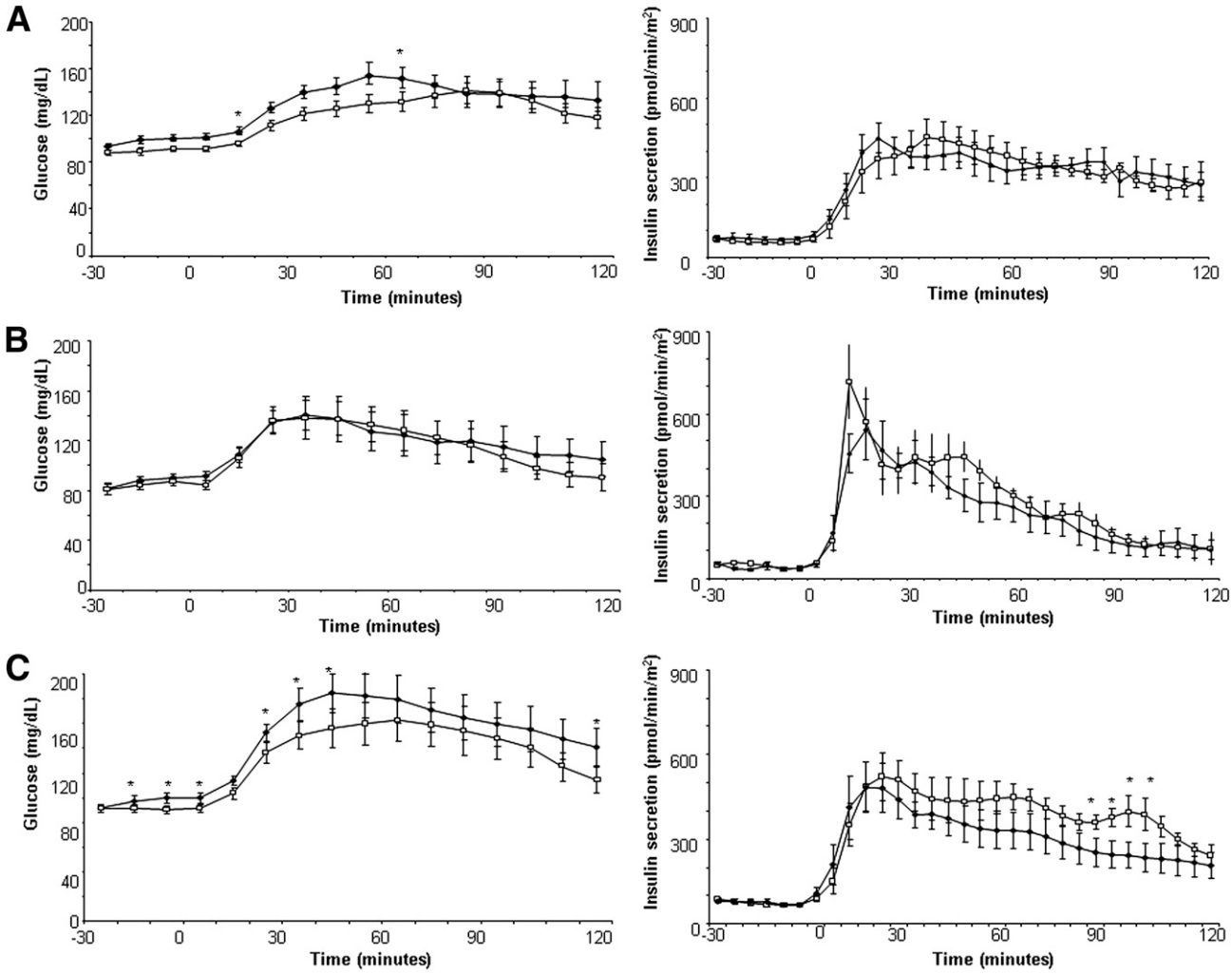

Figure 1—Blood glucose and insulin secretion in response to a SMLM during saline (□) or Ex 9-39 (◆) infusion in normal-weight NO-control subjects (*A*), nondiabetic SG-control subjects (*B*), and SG-DMR subjects (*C*). Data are presented as mean ± SEM. *$P < 0.05$ relative to the saline condition.

that enhanced GLP-1 secretion commonly described after SG is not the key determinant of the long-term beneficial effects of this type of surgery on T2DM.

Because of the well-established role of GLP-1 in glucose homeostasis and the parallel improvement in glucose tolerance, β-cell function, and GLP-1 response after SG in several association studies, a causative role of GLP-1 in the amelioration of glucose homeostasis commonly seen after SG has been proposed (1,11,12). According to this hypothesis, a larger incretin response should have been observed in SG subjects in remission in our study 1 compared with those with lack of T2DM remission. In contrast, in study 1, GLP-1 release was almost superimposable regardless of glucose tolerance status. Admittedly, postsurgical restoration of the GLP-1 response was an independent determinant of restored glucose tolerance in a recent prospective study of T2DM patients who had undergone SG or RYGB (11). Nonetheless, in line with our data, in that study the postsurgical GLP-1 response was not an independent predictor of glucose tolerance status. We also acknowledge data obtained in rodents suggesting that differences in the sensitivity to GLP-1 could be implicated in the effects of RYGB on glucose tolerance (13). Nonetheless, though limited by our cross-sectional design, the current association study supports the notion that GLP-1 secretion does not play a critical role in the outcome of T2DM after SG.

To circumvent the limitations inherent in association studies, we conducted study 2, in which glucose tolerance was evaluated with or without GLP-1 blockade. In support of the findings in study 1, GLP-1 blockade resulted in limited deterioration of glucose tolerance. In particular, in subjects in remission of T2DM the blockade resulted in only a 13.2 ± 15.9% increase in the glucose response, similar to the change seen in the NO-control group (10.1 ± 8.4%) ($P = 0.281$) (Table 3). These results are similar to those recently reported by our group and others in subjects in T2DM remission after RYGB (2,14).

Table 3—Glucose and insulin responses to a SMLM with or without Ex 9-39

	NO-control group (n = 8)		SG-control group (n = 6)		SG-DMR group (n = 8)			
	Saline	Ex 9-39	Saline	Ex 9-39	Saline	Ex 9-39	P_{group}	$P_{Ex\ 9\text{-}39}$
Glucose at −30 min (mg/dL)	88 ± 7	93 ± 5	81 ± 11	81 ± 13	91 ± 8	92 ± 8	<0.019	0.444
Glucose at 0 min (mg/dL)	92 ± 6	101 ± 9	84 ± 8	91 ± 10	92 ± 8	100 ± 12	0.130	<0.001
Peak glucose (mg/dL)	149 ± 28	170 ± 36	149 ± 39	150 ± 37	178 ± 18	196 ± 15	0.176	0.013
Time to peak glucose (min)	68 ± 26	56 ± 29	43 ± 20	32 ± 16	53 ± 10	38 ± 6	0.066	0.032
2-h glucose (mg/dL)	118 ± 25	133 ± 45	90 ± 29.5	105 ± 39	114 ± 31	141 ± 31	0.206	0.008
Mean glucose (mg/dL)	123 ± 18	135 ± 17	114 ± 28	118 ± 35	139 ± 32	156 ± 36	0.817	0.018
AUC glucose$_{0-120}$ ($mg \cdot dL^{-1} \cdot min \cdot 10^3$)	14.9 ± 2.2	16.3 ± 2.0	14.0 ± 3.4	14.4 ± 4.3	17.0 ± 1.4	19.1 ± 1.6	0.124	0.005
Insulin at −30 min (pmol/L)	45 ± 24	55 ± 43	51 ± 25	38 ± 19	77 ± 19	63 ± 22	0.142	0.232
Insulin at 0 min (pmol/L)	35 ± 19	47 ± 35	34 ± 16	36 ± 18	49 ± 13	45 ± 12	0.521	0.275
Mean insulin (pmol/L)	239 ± 110	243 ± 93	492 ± 228	350 ± 95	400 ± 158	309 ± 122	0.023	0.039
Fasting ISR ($pmol \cdot min^{-1} \cdot m^{-2}$)	69 ± 28	72 ± 26	50 ± 18	53 ± 13	88 ± 14	80 ± 14	0.013	0.892
Total insulin output ($nmol \cdot m^{-2}$)	41 ± 12	42 ± 8	36 ± 8	32 ± 8	49 ± 11	40 ± 11	0.132	0.017
β-Cell glucose sensitivity	151 ± 100	100 ± 56	91 ± 29	94 ± 42	120 ± 72	73 ± 46	0.512	0.008
Rate sensitivity ($nmol \cdot m^{-2} \cdot mmol/L$)	1.85 ± 1.62	1.30 ± 0.65	1.41 ± 1.02	1.48 ± 0.95	2.38 ± 1.08	2.27 ± 1.29	0.234	0.517
Potentiation factor	1.02 ± 0.40	1.31 ± 0.65	1.40 ± 1.01	1.48 ± 0.95	1.50 ± 0.32	1.37 ± 0.56	0.725	0.909

Data are expressed as means ± SD. ISR, insulin secretion rate.

Importantly, our subjects with postsurgical remission were also compared with a nondiabetic group that had undergone SG, thereby excluding anatomical differences as a potential source of confounding. Although the use of a mixed-meal challenge rather than a standard oral glucose tolerance test precluded formal assessment of glucose tolerance, under Ex 9-39 infusion only one of eight patients each in the SG-DMR and the NO-control group presented with 2-h glucose levels above the diagnostic threshold for T2DM.

In agreement with previous studies, in our studies β-cell function emerged as the dominant factor influencing the outcome at 2 years after surgery (11). The impairment in β-cell function found in study 1 is concordant with the altered insulin secretion after a meal challenge as well as intravenous glucose administration previously reported by our group in subjects who had undergone RYGB (4). Although the β-cell response to other stimuli was not tested in the current study, recent evidence consistently shows that residual β-cell function is required for a sustained beneficial effect of RYGB on glucose tolerance even in the context of marked GLP-1 secretion (15). Of note, in study 2 Ex 9-39 was associated with a significant decrease in insulin secretion and total insulin output in both surgical groups, supporting the notion that GLP-1 does potentiate insulin secretion after SG and RYGB (16). Nonetheless, the limited impact of the GLP-1 blockade on both insulin secretion and glucose tolerance after SG suggests that other factors are important.

Rapid gastric emptying could be viewed as a potentially unifying mechanism for the hormonal changes after SG. In a recent study in a rodent model, Chambers et al. (17) demonstrated that SG causes accelerated emptying of gastric contents into the intestine and failure to respond to many of the regulatory signals that normally control gastric emptying rate, including GLP-1. On the other hand, postprandial hyperglucagonemia, such as that found in our studies (11,12), has also been described after pharmacological or surgical acceleration of gastric emptying in human subjects (18,19). Although the mechanism(s) underlying this phenomenon remain unclear, it has been hypothesized that rapid increases in portal vein glycemia—due to accelerated intestinal glucose flux—could activate portal glucose sensors influencing neural regulation of α-cell activity (20). Under these circumstances, the enhanced GLP-1 response after SG could be aimed not only, or not so much, to potentiate insulin secretion but also, or primarily, to restore gastric motility. On the other hand, the paradoxical rise in glucagon release in SG-operated subjects may result from signal(s) overriding the normal regulation of the α-cell, which our Ex 9-39 results suggest is at least partly retained postsurgery.

Within its limitations (the cross-sectional design, use of a mixed meal rather than an oral glucose tolerance test, lack of measures of gastric emptying, and other physiological determinants of glucose tolerance), the current study is the first to analyze the contribution of GLP-1 to glucose tolerance after SG using an outcome and a GLP-1 blockade protocol. Although our data do not rule out a role of GLP-1 in improving glucose tolerance shortly after surgery (11,12) and sustaining weight loss (21), they strongly suggest

that at a time when weight loss after SG has occurred, the impact of GLP-1 on glucose tolerance is limited.

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