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Evidence from a single individual that increased plasma GLP-1 and GLP-1-stimulated insulin secretion after gastric bypass are independent of foregut exclusion

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To the Editor

Gastric bypass surgery (GB) has profound effects on glucose tolerance and insulin secretion that are often present before significant weight loss [1]. These effects have been attributed to changes in glucose fluxes through the reconfigured gastrointestinal (GI) tract [2, 3], and increased secretion and action of glucagon-like peptide 1 (GLP-1) [4–7]. GB causes an earlier, higher peak of glucose as well as a lower nadir after food intake[8], likely the result of rapid transit of nutrients from the gastric pouch into the small intestine [2, 3, 9]. However, it is unclear whether increased GLP-1 secretion and action after GB is also due to rapid flow of nutrients from the gastric remnant to the intestine, as is often proposed. We report here the effects of the GLP-1 receptor antagonist exendin-(9–39) (Ex-9) in an individual with GB during oral intake or feeding through a gastrostomy tube (GT), conditions bypassing or including the foregut. We predicted that reduced meal-derived glucose appearance as a result of nutrient passage through the foregut would diminish GLP-1 secretion and action.

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Contribution statement

MS designed and supervised the study, obtained the data, analysed and interpreted the data and wrote the manuscript. AG contributed to data analysis, interpretation, presentation and review. DAD contributed to interpretation of data and review/editing of the manuscript. MS as the guarantor takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript. The manuscript was revised and approved by all authors.

Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

We compared the effect of nutrient passage through the remnant stomach or gastric pouch on glucose flux and insulin and GLP-1 secretion in a weight-stable GB patient with a GT placed for clinical reasons (electronic supplementary material [ESM] Fig. 1). This patient was studied in matched experiments with and without infusion of Ex-9 to determine GLP-1 action. Although questions as to the specificity of Ex-9 as a GLP-1 receptor (GLP-1r) antagonist have been raised by in vitro and animal studies, in humans Ex-9 has been demonstrated to block exogenous GLP-1 with no effect on the insulinotropic action of glucose-dependent insulinotropic peptide (GIP) [10]. For comparison we used a group of glucose-tolerant individuals with no history of GI surgery (CON) who also had similar meal tests with and without Ex-9 [4] (see ESM Methods). The glucose responses to meal ingestion and the systemic appearance of ingested glucose (Ra_{Oral}) were shifted to the left and upwards during the oral test meal in the surgical patient compared with the controls, whereas the 3 h glucose AUC did not differ (Fig. 1, Table 1). In the GB patient, administration of the meal per mouth (GB-oral) caused a larger and earlier glucose response, faster Ra_{Oral} and a lower glucose nadir compared with the responses following GT feeding (GB-GT), but $AUC_{Glucose(0-180min)}$ was not different (Fig. 1, Table 1). Moreover, overall glucose AUC and Ra_{Oral} during the saline study were comparable with those of controls in the GB-GT study. GLP-1r blockade increased the early systemic appearance of ingested glucose in the GB patient and control individuals (Fig. 1, Table 1). Blocking the GLP-1r attenuated the postprandial drop in glucose level in the GB-oral study, similar to recent findings reported in another cohort of GB patients [4] (Fig. 1).

Similar to the changes in blood glucose and Ra_{Oral} , prandial insulin secretion was higher when the GB patient ate the test meal, with the largest effect in the first 30 min (Fig. 1). Compared with the GT administration of nutrients, oral feeding led to a fivefold increase in the area under the insulin curve, $AUC_{Insulin(0-30min)}$, and a twofold increase in the area under the insulin secretion rate (ISR) curve, $AUC_{ISR(0-30min)}$ (Fig. 1, Table 1). Despite higher fasting insulin concentrations, the non-surgical control individuals had a 3 h postprandial beta cell output that was similar to that of the GB patient with the GT meal (Fig. 1, Table 1). GLP-1r blockade had a similar relative effect in decreasing insulin secretion during oral and GT feedings (60–70%) in the surgical subject, but this effect was substantially less (~20%) in the controls (Fig. 1). The meal tolerance test-derived insulin sensitivity (oral glucose insulin sensitivity index $[OGIS]_{120min}$) was similar between the GB patient and the controls and was not affected by the route of meal administration or GLP-1r blockade (Table 1).

The GB patient had plasma GLP-1 levels that were substantially greater than the controls, both during oral and GT feeding (Fig. 1, Table 1). The overall GIP response to meal ingestion was not significantly different between the oral and GT feedings in the surgical patient (ESM Fig. 2). The postprandial glucagon responses were greater in the GB patient than in the controls, particularly when meal was administered orally, and minimally affected by Ex-9 infusion (Table 1, ESM Fig. 3). The postprandial response of pancreatic polypeptide (PP) was larger in the GB patient than in the controls, and was twice as high with oral than with GT feeding (Table 1, ESM Fig. 3). In the GB patient postprandial symptoms were increased significantly with oral compared with GT feeding and non-GI

symptoms were eliminated significantly as a result of GLP-1r blockade during both oral and GT feedings.

In this paper we describe a set of observations that were made possible by the availability of a weight-stable individual with an intact gastric tube 8 years after GB. The meal studies demonstrated that oral consumption in the GB patient caused a large, rapid flux of intestinal glucose, with prandial hyperglycaemia and a lower glucose nadir that is characteristic of GB [2, 3, 8, 9]. Coincident with this were exaggerated excursions of ISR and GLP-1, also typical in post-surgical patients [7, 8]. The glucose and Ra_{Oral} responses to the test meal were muted when our GB patient was fed through the GT. Nonetheless, plasma GLP-1 concentrations and the augmentation of insulin secretion by GLP-1 remained substantially higher than in the control individuals. These findings suggest that GB alters the secretion and action of GLP-1, independent of the route of nutrient entrance into the gut.

There have been several previous comparisons of oral and GT feeding in GB patients, including a single case [11] and three collections of four, five and nine patients [12–14]. Similar to our patient, plasma glucose and insulin were significantly greater with oral than with GT administration of nutrients. However, in contrast to our results, plasma GLP-1 was only higher when the test meal was ingested and was lower when nutrients were given by GT [11–13]. The reason for this difference is not clear, although in two of these reports the individuals were studied in the postoperative period [12, 13] and they may not have been fully adapted to the GB. Our patient had GLP-1 levels that were 10- to 15-fold those of the control group with oral or GT feedings. Importantly this effect was noted even during the GT meal with saline when $AUC_{Glucose(0-180min)}$ and 2 h Ra_{Oral} were similar to those of the controls. This raises the possibility that increased GLP-1 release in GB patients is not entirely due to rapid nutrient passage into the mid- and distal-gut as is commonly believed. It is plausible that the distribution and function of neuroendocrine cells producing gut hormones are modified after GI surgeries [15, 16], such that GLP-1 secretion is increased independent of nutrient digestion and absorption. It is not surprising that with massive elevations of prandial GLP-1 the effect of GLP-1 to stimulate plasma insulin was two- to threefold greater in the GB patient; it seems reasonable to presume that higher plasma GLP-1 after GB is associated with greater GLP-1-stimulated insulin secretion [4, 6].

While plasma GLP-1 was elevated with both oral and GT feeding, we noted increased postprandial glucagon and PP when the foregut was excluded from meal contents. Elevated plasma glucagon after GB has been a consistent finding [4, 7] and, taken in conjunction with increased PP, raises the possibility of increased parasympathetic responses to rapid nutrient entry into the intestine. Postprandial symptoms after gastroenterostomy was described as early as 1913 [17] and later attributed to rapid drainage of stomach and was termed dumping [18]. We have shown here that excluding the foregut increases both GI and non-GI symptoms associated with altered glucose and hormonal profile. It is unclear whether dumping symptoms contribute to islet function through altered neural activity, but given the elevated levels of PP and glucagon after meal ingestion by our patient this is plausible. Of note, our findings demonstrate that blocking the GLP-1r reduced non-GI dumping symptoms during oral feeding, but had no effect on alimentary symptoms, suggesting that alimentary and systemic symptoms of dumping have a different underlying pathogenesis.

The conclusions from this set of experiments are limited because of their dependence on data from a single individual; it is possible that this individual has unique features that are not generalisable to most GB patients. Certainly her BMI at the time of these studies was much lower than that of the vast majority of patients several years after GB. However, there is no evidence that differences in body weight have significant effects on GLP-1 secretion. Moreover, our patient's prandial glucose, insulin and GLP-1 responses, as well as the effect of Ex-9, are very similar to what has been reported in other GB patients after test meals [2, 3, 8, 9]. Finally, the key findings in these studies, that the GB patient had increased plasma GLP-1 concentrations and GLP-1 action independent of the route of feeding, are based on differences from the control individuals that are sufficiently distinct to be unlikely due to chance alone.

The results of this case study are in keeping with previous results indicating an increased role for GLP-1 in the insulin response following GB [4–7]. They also suggest that activation of GLP-1 release is not entirely due to rapid passage of nutrients into the lower gut, often referred to as the 'hindgut hypothesis'. These findings need to be replicated in larger samples, but raise the possibility of novel effects of GB on enteroendocrine function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CON	Non-operated controls with normal glucose tolerance
Ex-9	Exendin-(9–39)
GB	Gastric bypass surgery
GB-GT	Studies with administration of meal per GT in the GB patient
GB-oral	Studies with administration of meal per oral in the GB patient
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide 1

GLP-1r	GLP-1 receptor
GT	Gastrostomy tube
ISR	Insulin secretion rate
OGIS	Oral glucose insulin sensitivity index
PP	Pancreatic polypeptide
Ra_{Oral}	Systemic appearance of ingested glucose

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Fig. 1.

Blood glucose concentration (a), Ra_{Oral} (b), GLP-1 concentration (c) and ISR after meal ingestion (d) in the GB patient, with oral and GT feedings, and in a historic group of non-surgical controls (CON-oral) during studies with (dashed lines, white bars) and without (solid lines, black bars) Ex-9 infusion. Corresponding AUC and GLP-1 contribution to insulin secretion response are shown as insets; percentages in insets show GLP-1 effects

Glucose, GLP-1 and islet cell response to meal ingestion per mouth (oral) or per GT in studies with and without intravenous Ex-9 infusion in the GB patient compared with a historical group of non-surgical controls (CON)

Table 1

Variable	Time (min)	GB-oral		GB-GT		CON-oral		GB-oral/GB-GT ^a	GB-GT/CON-oral ^b
		Saline	Ex-9	Saline	Ex-9	Saline	Ex-9		
AUC _{Glucose} (mmol/l × min)	0–30	151	121	34	71	12 ± 3	45 ± 1	4.4	3.0
	0–60	255	187	90	108	57 ± 5	90 ± 5	2.8	1.6
	0–180	205	203	185	155	210 ± 18	216 ± 20	1.1	0.9
AUC _{RaOral} (μmol/kg)	0–30	1,583	2,346	494	1,672	208 ± 27	313 ± 79	3.2	2.4
	0–60	1,765	2,244	683	1,856	544 ± 35	644 ± 109	2.6	1.3
	0–120	1,903	2,007	1,003	2,202	1,107 ± 55	1,057 ± 149	1.9	0.9
AUC _{Insulin} (nmol/l × min)	0–30	71.6	23.0	13.9	11.1	4.9 ± 1.9	4.7 ± 1.0	5.1	2.9
	0–60	130.8	31.7	32.8	14.9	18.6 ± 6.1	15.3 ± 2.7	4.0	1.8
	0–180	143.5	36.5	50.3	17.9	55.7 ± 13.5	43.3 ± 6.5	2.9	0.9
AUC _{ISR} (nmol)	0–30	56.5	28.7	27.4	11.7	9.5 ± 3.2	11.3 ± 2.4	2.1	2.9
	0–60	141.6	49.6	50.7	22.6	30.1 ± 8.6	24.9 ± 4.3	2.8	1.7
	0–180	159.5	61.5	90.1	30.1	80.4 ± 14.8	62.2 ± 9.1	1.8	1.1
AUC _{GLP-1} (nmol/l × min)	0–30	13.2	21.6	9.4	11.0	0.3 ± 0.1	0.8 ± 0.1	1.4	29.3
	0–60	29.5	45.4	23.9	21.4	1.1 ± 0.4	2.4 ± 0.2	1.2	20.9
	0–180	45.7	64.9	44.9	31.9	3.3 ± 0.9	6.5 ± 0.7	1.0	13.7
AUC _{Glucagon} (ng/l × min)	0–60	1,802	1,800	931	1,101	–16 ± 234	522 ± 56	1.9	–58.8
	0–180	6,000	4,226	3,814	3,426	–893 ± 704	1,177 ± 84	1.6	–4.3
AUC _{pp} (% × min)	0–60	787		343		122 ± 33		2.3	2.8
	0–180	1,240		666		240 ± 58		1.9	2.8
OGIS (ml min ^{–1} m ^{–2})	0–120	458	459	376	439	406 ± 19	393 ± 12	1.2	0.9

Data are presented as mean ± SEM for CON-oral studies

^a Effect of foregut bypass in the surgical patient, calculated as AUC_{Outcome} GB-oral / AUC_{Outcome} GB-GT during saline studies

^b Effect of route of feeding per remnant stomach in the surgical patient compared with per oral in the controls, computed as AUC_{Outcome} GB-GT / AUC_{Outcome} CON-oral during saline studies