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Effect of sitagliptin on glucose control in type 2 diabetes mellitus after Roux-en-Y gastric bypass surgery

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Abstract

The present study was a 4-week randomized trial to assess the efficacy and safety of sitagliptin, a dipeptidyl-peptidase-4 inhibitor, in persistent or recurring type 2 diabetes after Roux-en-Y gastric bypass surgery (RYGB). Participants (n = 32) completed a mixed meal test (MMT) and self-monitoring of plasma glucose (SMPG) before and 4 weeks after randomization to either sitagliptin 100 mg daily or placebo daily. Questionnaires were administered to assess gastrointestinal discomfort. Outcome variables were glucose, active glucagon-like peptide-1 and β -cell function during the MMT, and glucose levels during SMPG. Age (56.3 ± 8.2 years), body mass index (34.4 ± 6.7 kg/m²), glycated haemoglobin ($7.21 \pm 0.77\%$), diabetes duration (12.9 ± 10.0 years), years since RYGB (5.6 ± 3.3 years) and β -cell function did not differ between the placebo and sitagliptin groups at pre-intervention. Sitagliptin was well tolerated, decreased postprandial glucose levels during the MMT (from 8.31 ± 1.92 mmol/L to 7.67 ± 1.59 mmol/L, $P = 0.03$) and mean SMPG levels, but had no effect on β -cell function. In patients with diabetes and mild hyperglycemia after RYGB, a short course of sitagliptin provided a small but significant glucose-lowering effect, with no identified improvement in β -cell function.

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Conflict of interest

None declared.

Author contributions

A. S. contributed to data analysis and interpretation and drafted and edited this manuscript. K. L. contributed to data collection, analysis and interpretation and edited the manuscript. A. S. and K. L. contributed equally to the manuscript. E. P., B. R., M. A., S. S., M. H., R. D., participated in data collection and edited the manuscript. S. B. and J. M. referred participants and edited the manuscript. B. L. designed the study, supervised the data analysis, interpreted the data and wrote and edited the manuscript. B. L. is the guarantor of this work, and, as such, had full access to all the data and take responsibility for the integrity of the data and accuracy of the data analysis.

Prior presentation

Part of this work was presented as an oral presentation at the American Diabetes Association Meeting in San Diego, CA in June 2017.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Keywords

dipeptidyl-peptidase 4 inhibitor; gastric bypass; type 2 diabetes

1 | INTRODUCTION

Approximately 60% of individuals experience type 2 diabetes (T2DM) remission after Roux-en-Y gastric bypass surgery (RYGB).¹ Along with weight loss, incretins may play a part in diabetes remission after RYGB.² Blocking the glucagon-like peptide-1 (GLP-1) receptor with exendin₉₋₃₉ reverses the effect of RYGB on β -cell function and glucose tolerance.³ The treatment of T2DM recurrence after surgery can be challenging, given the potential for dumping syndrome, reactive hypoglycaemia and fear of weight regain. Inhibitors of dipeptidyl peptidase-4 (DPP-4), the enzyme that inactivates GLP-1,⁴ are commonly used for the treatment of T2DM, are well tolerated and weight-neutral.⁵ It is unknown whether the addition of DPP-4 inhibitors would improve glucose control after RYGB where elevated GLP-1 levels² and decreased DPP-4 activity⁶ already exist.

The aim of the present study was to assess the efficacy and safety of a short course of the DPP-4 inhibitor sitagliptin in patients with persisting and/or recurrent T2DM at least 12 months after RYGB.

2 | METHODS

The trial was registered with the clinical trial registration number: NCT01512797.

Participants were recruited from a pool of eligible patients with T2DM who underwent RYGB at St Luke's Hospital, between 2000 and 2011, or via direct physician referral (for recruitment strategy see Supporting Information). Informed consent was obtained from all patients prior to participation. Experimental procedures were conducted at the Columbia University Clinical Research Center between 2012 and 2016. This was an individual randomized (1:1), double-blind, 2-group, parallel longitudinal study in which participants were randomized to receive daily sitagliptin 100 mg daily or placebo for 4 weeks.

Participants came in for 2 study visits after the screening, before and 4 to 5 weeks after starting the study drug, and received a standardized 200 kcal liquid mixed meal test (MMT; 55% carbohydrates [Boost; Nestle Health Science, Bridgewater, New Jersey]). Fasting venous blood samples were obtained to assess fructosamine, and fasting and at 15, 30, 60, 90, 120 and 180 minutes during the MMT for glucose, GLP-1, insulin and C-peptide levels. A home 7-point plasma glucose profile by finger stick (self-monitoring of plasma glucose [SMPG]) was self-collected before and at 4- to 5-week follow-up. Assessment of hunger, fullness and stomach discomfort on a 150-mm visual analogue scale (VAS),⁷ and of dumping syndrome with the Sigstad clinical diagnostic index⁸ was carried out during the MMT before and at the end of the 4-week intervention.

Blood was collected in 2 chilled EDTA tubes, 1 tube containing both aprotinin (500 kallikrein inhibitory units/mL of blood) and DPP-4 inhibitor (10 μ L/mL of blood, Millipore

Research, Billerica, Massachusetts) for measurement of active GLP-1 and the other tube containing no additives. Glucose was measured using the glucose oxidase method (Analox Instruments, Lunenburg, Massachusetts). Active GLP-1 levels (enzyme-linked immunosorbent assay; Alpco, Salem, New Hampshire), insulin and C-peptide levels (radioimmunoassay; Millipore), and fructosamine (automated chemistry analyser; Roche, Indiana, Indianapolis) were measured for all participants except one.

2.1 | Statistical analysis

Data are expressed as mean $\pm$ standard deviation, except in the Figures, where data are expressed as mean $\pm$ standard error of the mean.

Area under the curve (AUC) was calculated using the trapezoidal rule. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as (fasting insulin [mU/L] $\times$ fasting glucose [mmol/L])/22.5, and homeostatic model assessment of β -cell function (HOMA- β) as $([20 \times \text{fasting insulin } \{\mu\text{IU/mL}\}]/[\text{fasting glucose } \{\text{mmol/L}\}-3.5])$.⁹ Insulin secretion rates (ISR, pmol/kg/min) were calculated with a mathematical C-peptide deconvolution method using a 2-compartment model from the MMT.¹⁰ β -cell glucose sensitivity (β CGS, pmol/kg/min/mM) was calculated as the slope between ISR and corresponding glycaemia from baseline to peak glucose levels. The disposition index (DI) was calculated using the formula $\beta\text{CGS} \times (1/\text{HOMA-IR})$.

The primary endpoint was glucose levels during the MMT and SMPG. Secondary endpoints were active GLP-1 levels and β -cell function (ISR, β CGS, DI). Generalized linear model (GLM) with repeated measures was performed to test each treatment effect (placebo or sitagliptin) on outcome variables during the MMT, and to test for difference between groups during the MMT before and after the intervention. In addition, paired t-tests for within-group and unpaired t-tests for between-group differences were performed to compare AUC, β CGS and DI. spss 24 (IBM, Armonk, NY) was used and P values $<.05$ (two-tailed) were taken to indicate statistical significance.

2.2 | Power analysis

Based on the effect of DPP-4 inhibitors in non-operated participants with type 2 diabetes, showing a significant decrease in 120-minute postprandial glucose by 1.67 ± 0.98 mmol/L after an MMT, we estimated that a sample size of 16 participants per group would show postprandial glucose differences between the placebo and sitagliptin group with $\alpha = .05$ for a power $> 90\%$.¹¹

3 | RESULTS

3.1 | Subject characteristics

Age, BMI, glycated haemoglobin (HbA1c), diabetes duration prior to RYGB, years since RYGB, fasting and peak glucose levels, AUC of glucose, 120-minute glucose levels, SMPG values, fasting and peak active GLP-1 levels, AUC of active GLP-1, HOMA- β , ISR, β CGS or DI values did not differ between the placebo and sitagliptin groups prior to intervention (Table 1 and Appendix S1).

3.2 | Glucose control

After intervention, the 120-minute glucose level decreased significantly during the MMT only after sitagliptin (8.31 ± 1.92 to 7.67 ± 1.59 mmol/L; $P = .03$ [Table 1 and Figure 1B]).

The average SMPG values decreased significantly with sitagliptin (7.93 ± 2.05 to 6.93 ± 1.30 mmol/L; $P = .03$), while increasing significantly with placebo (6.71 ± 1.10 to 7.25 ± 1.30 mmol/L; $P = .04$). The change in fructosamine () was significantly different between the groups (placebo: 7.13 ± 25.62 μ mol/L; sitagliptin: -13.53 ± 30.35 μ mol/L; $P = .05$), demonstrating a benefit of sitagliptin (Table 1).

To assess the role of diabetes control in the effect of sitagliptin, a sub-analysis was performed on individuals with HbA1c > 7.0% ($n = 16$; placebo, $n = 6$; sitagliptin, $n = 10$) and on those with HbA1c $\leq 7.0\%$. Sitagliptin decreased fasting and 120-minute glucose levels during the MMT, mean glucose levels during SMPG, and fructosamine levels only in the participants with worse diabetes control (data not shown).

3.3 | β -cell function

The HOMA- β , ISR, β CGS or DI values post-intervention, or their change with intervention, did not differ between treatment groups (Table 1 and Figure 1C–F).

3.4 | Active GLP-1 levels

Peak and 120-minute active GLP-1 increased significantly more during the MMT administered after treatment with sitagliptin compared with placebo (Figure 1G,H). There were no correlations between fasting or peak active GLP-1 concentrations and fasting or 120-minute glucose concentrations, respectively, in either intervention group, before or after intervention (data not shown).

3.5 | Safety and tolerability

Sitagliptin was well tolerated and there were no differences in Sigstad values or VAS scores taken during the MMT between groups and/or within each intervention (data not shown).

4 | DISCUSSION

This is the first study to test the safety and efficacy of a short course of a DPP-4 inhibitor in individuals with T2DM after RYGB. The main finding of this study is that sitagliptin 100 mg taken daily for 4 to 5 weeks had a small but significant effect on lowering postprandial glucose values, without observed improvement in β -cell function. Sitagliptin was well tolerated and did not cause hypoglycaemia.

Svane et al.¹² looked at the acute effect of a single dose of oral sitagliptin 100 mg, vs placebo, given a short time before an MMT in normal glucose-tolerant individuals after RYGB. In that study, sitagliptin resulted in a small decrease in peak glucose levels in response to the MMT but did not change glucose AUC or 120-minute glucose levels. Intact GLP-1 levels increased with sitagliptin in their RYGB cohort, similarly to our findings, suggesting a proper absorption of sitagliptin. The present study, in individuals with T2DM,

and the study by Svane et al., in normal glucose-tolerant individuals, showed that the effect of DPP-4 inhibition on glucose after RYGB was of small magnitude, despite a distinct effect on active GLP-1 levels. This could be related to the already elevated postprandial incretin levels after RYGB.²

In a similar vein, Nauck et al.¹³ studied sitagliptin given 60 minutes prior to an MMT in non-operated individuals treated with the GLP-1 agonist liraglutide and with metformin. Their data showed higher levels of intact GLP-1 and gastric inhibitory polypeptide concentrations after sitagliptin, but without added benefit with regard to glycaemic control. The authors proposed that GLP-1 receptors were already maximally stimulated by liraglutide therapy, leaving little room for benefit to be achieved with the addition of sitagliptin.¹³ There may be a comparable situation after RYGB, in which maximal postprandial levels of GLP-1 already exist.

The International Diabetes Federation now recommend bariatric surgery, including RYGB, as a part of the algorithm in T2DM management in individuals with severe obesity.¹⁴ In spite of its effect on glucose metabolism, bariatric surgery does not provide a long-lasting “surgical cure” of T2DM, as relapse occurs in one-third of patients 5 to 8 years after RYGB.¹⁵ The change in meal pattern, with multiple smaller meals, the fear of weight regain and the presence of dumping syndrome, with or without reactive hypoglycaemia, make the treatment of T2DM after RYGB challenging. DPP-4 inhibitors are an attractive option as they are well tolerated, weight-neutral and rarely cause hypoglycaemia; however, these data suggest that sitagliptin, although well tolerated, has minimal efficacy on glucose or fructosamine levels and adds little benefit in patients with well-controlled T2DM after RYGB.

The efficacy of sitagliptin was modest in the present selected group of individuals compared with non-operated individuals with T2DM, and compared with the effect of RYGB itself. Fasting glucose levels have been shown to decrease by -7.4% after sitagliptin alone,¹⁶ by -19.2% after RYGB alone,¹⁷ and by -9.3% (not significant) in the present study with sitagliptin after RYGB. The magnitude of the effect of RYGB alone has also been demonstrated, with a greater suppression (-35.1%) of 120-minute glucose after surgery,¹⁷ twice as great as after DPP-4 inhibition alone in non-operated patients (-18.2%),¹⁶ while decreasing only by -9.5% ($P < .05$) in the present study.

The severity of the T2DM, assessed by usage of insulin or level of HbA1c, may affect the response to DPP-4 inhibition. Our subanalysis points to a larger effect of sitagliptin on glucose in individuals with poorer control prior to intervention (ie, HbA1c >7%), similar to the results observed in other diabetes intervention trials.¹⁸

The strengths of the present study include the randomized placebo-controlled design, the unique study population, the measurement of glucose levels in the home setting as well as in the clinical research centre, and the assessment of active GLP-1 levels and β -cell function during an MMT. Limitations of the study include its short duration and its proof-of-concept design, rather being a large clinical trial. All participants had undergone RYGB, and we cannot extrapolate our findings to other bariatric surgeries, such as adjustable gastric banding or vertical sleeve gastrectomy. Finally, the groups were small and the data cannot be

extrapolated to a larger group of individuals with a wide range of diabetes control; however, participants for studies such as this one are difficult to recruit, and are understudied, and we believe these data, even though derived from a small cohort, are valuable.

In conclusion, sitagliptin was safe and led to a modest improvement in glucose and fructosamine concentrations, compared with placebo, in individuals with T2DM after RYGB. The effect of sitagliptin is more pronounced in individuals with worse control prior to initiation of treatment. The treatment was not accompanied by measurable improvement in β -cell function. The small magnitude of the effect of sitagliptin on glucose after RYGB is similar to that which is observed when adding sitagliptin to existing GLP-1 agonist treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Effect of an MMT on glucose, active GLP-1, ISR and C-peptide after placebo or sitagliptin. Glucose (mmol/L) before and after placebo (A) and before and after sitagliptin (B). Active GLP-1 concentrations (pmol/L) before and after placebo (C) and before and sitagliptin (D). ISR in pmol/kg/min before and after placebo (E) and before and after sitagliptin (F). Black symbols are pre-intervention, open symbols are post-intervention. * $P < .05$ vs prior to intervention within each group

TABLE 1
Effect of intervention on glucose, active GLP-1 levels and markers of β -cell function

	Placebo		Sitagliptin		P		
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention			
MMT fasting glucose, mmol/L	6.52 ± 1.21	6.39 ± 1.23	-0.17 ± 0.87	7.10 ± 1.74	6.44 ± 1.25	-0.62 ± 1.32	.27
MMT average glucose, mmol/L	8.12 ± 1.14	7.86 ± 1.04	-0.26 ± 0.82	8.55 ± 1.95	7.84 ± 1.47	-0.71 ± 1.56	.31
MMT peak glucose, mmol/L	10.62 ± 1.28	10.54 ± 1.11	-0.08 ± 1.01	11.26 ± 2.58	10.74 ± 1.85	-0.51 ± 1.92	.42
MMT glucose AUC, min/mmol/L	7.96 ± 1.20	7.75 ± 1.16	-0.21 ± 0.89	8.31 ± 1.92	7.67 ± 1.59	-0.64 ± 1.40	.31
MMT 120-min glucose, mmol/L	7.01 ± 1.38	6.97 ± 1.47	-0.04 ± 1.02	7.51 ± 1.91	6.79 ± 1.65	-0.72 ± 1.18*	.09
AUC ISR, pmol/kg/min	412.5 ± 181.8	373.2 ± 160.5	-39.36 ± 69.80*	368.9 ± 112.6	380.7 ± 114.8	11.82 ± 64.43	.06
Peak ISR, pmol/kg/min	5.07 ± 2.86	4.49 ± 2.60	-0.57 ± 1.31	4.53 ± 2.02	4.30 ± 1.91	-0.23 ± 1.60	.51
HOMA-IR	4.87 ± 4.86	4.31 ± 3.75	-0.54 ± 1.69	3.25 ± 1.63	2.76 ± 1.85	-0.66 ± 1.70	.85
HOMA-β, %	72.57 ± 41.83	75.94 ± 33.31	3.37 ± 30.33	70.50 ± 43.55	69.37 ± 29.99	-1.13 ± 35.93	.73
βCGS, pmol/kg/min/mmol	0.93 ± 0.65	0.71 ± 0.48	-0.21 ± 0.45	0.77 ± 0.40	0.75 ± 0.51	-0.02 ± 0.44	.24
DI	0.34 ± 0.26	0.27 ± 0.22	-0.06 ± 0.21	0.32 ± 0.028	0.38 ± 0.35	0.07 ± 0.35	.22
Fasting C-peptide, ng/mL	1.43 ± 0.41	1.45 ± 0.45	0.014 ± 0.37	1.19 ± 0.68	1.22 ± 0.60	0.02 ± 0.36	.95
Peak C-peptide, ng/mL	3.70 ± 1.74	3.60 ± 1.31	-0.107 ± 1.11	3.48 ± 2.0	3.09 ± 1.56	-0.39 ± 0.97	.46
AUC C-Peptide, ng/mL/min	436.4 ± 147.4	440.5 ± 125.0	4.10 ± 86.27	399.8 ± 208.0	369.0 ± 172.4	-30.78 ± 89.8	.28
Fasting active GLP-1, pmol/L	2.95 ± 3.14	2.73 ± 2.59	-0.22 ± 0.88	5.40 ± 10.79	6.86 ± 9.43	1.45 ± 2.59*	.03
Peak active GLP-1, pmol/L	21.73 ± 15.51	24.70 ± 12.60	2.97 ± 10.44	21.04 ± 11.91	43.11 ± 24.43	22.08 ± 15.46*	<.01
AUC active GLP-1, pmol/L/min	1061.2 ± 656.1	1098.2 ± 591.0	36.97 ± 341.7	876.98 ± 355.87	2299.25 ± 1508.88	1422.3 ± 1391.6	.01

	Placebo		Sitagliptin		P		
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention			
Fructosamine, $\mu\text{mol/L}$	246.2 $\pm$ 43.3	253.3 $\pm$ 40.4	7.13 $\pm$ 25.62	257.7 $\pm$ 49.2	244.2 $\pm$ 32.3	-13.53 $\pm$ 30.35	.05
Fasting SMPG, mmol/L	6.05 $\pm$ 1.14	5.93 $\pm$ 1.20	-0.12 $\pm$ 1.13	6.52 $\pm$ 1.78	6.49 $\pm$ 1.73	0.38 $\pm$ 2.30	.44
Average SMPG, mmol/L	6.71 $\pm$ 1.10	7.25 $\pm$ 1.30	0.55 $\pm$ 0.98*	7.93 $\pm$ 2.05	6.93 $\pm$ 1.30	-1.00 $\pm$ 1.68*	.003

* $P < .05$ difference between pre- and post-intervention values within each group. P value reported is difference between change () with placebo vs change with sitagliptin.