

Clinical Research Article

# Gastrointestinal Hormones and $\beta$ -Cell Function After Gastric Bypass and Sleeve Gastrectomy: A Randomized Controlled Trial (Oseberg)

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**Abbreviations:**  $\beta$ -GS,  $\beta$ -cell glucose sensitivity; BMI, body mass index;  $C_{max}$ , peak concentration; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin A1c; iAUC, incremental area under the curve; ISR, insulin secretion rate; OGTT, oral glucose tolerance test; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

Received: 7 May 2021; Editorial Decision: 30 August 2021; First Published Online: 31 August 2021; Corrected and Typeset: 24 September 2021.

## Abstract

**Context:** Whether Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) differentially affect postprandial gastrointestinal hormones and  $\beta$ -cell function in type 2 diabetes remains unclear.

**Objective:** We aimed to compare gastrointestinal hormones and  $\beta$ -cell function, assessed by an oral glucose tolerance test (OGTT) 5 weeks and 1 year after surgery, hypothesizing higher glucagon-like peptide-1 (GLP-1) levels and greater  $\beta$ -cell response to glucose after RYGB than after SG.

**Methods:** This study was a randomized, triple-blind, single-center trial at a tertiary care center in Norway. The primary outcomes were diabetes remission and IVGTT-derived  $\beta$ -cell function. Participants with obesity and type 2 diabetes were allocated (1:1) to RYGB

or SG. We measured gastrointestinal hormone profiles and insulin secretion as  $\beta$ -cell glucose sensitivity ( $\beta$ -GS) derived from 180-minute OGTTs.

**Results:** Participants were 106 patients (67% women), mean (SD) age 48 (10) years. Diabetes remission rates at 1 year were higher after RYGB than after SG (77% vs 48%;  $P = 0.002$ ). Incremental area under the curve (iAUC<sub>0-180</sub>) GLP-1 and  $\beta$ -GS increased more after RYGB than after SG, with 1-year between-group difference 1173 pmol/L\*min (95% CI, 569-1776;  $P = 0.0010$ ) and 0.45 pmol/kg/min/mmol (95% CI, 0.15-0.75;  $P = 0.0032$ ), respectively. After surgery, fasting and postprandial ghrelin levels were higher and decremental AUC<sub>0-180</sub> ghrelin, iAUC<sub>0-180</sub> glucose-dependent insulintropic polypeptide, and iAUC<sub>0-60</sub> glucagon were greater after RYGB than after SG. Diabetes remission at 1 year was associated with higher  $\beta$ -GS and higher GLP-1 secretion.

**Conclusion:** RYGB was associated with greater improvement in  $\beta$ -cell function and higher postprandial GLP-1 levels than SG.

**Key Words:** gastric bypass, sleeve gastrectomy, gastrointestinal hormones, glucagon-like peptide 1, type 2 diabetes, obesity

Bariatric surgery significantly improves glycemic control in patients with obesity and type 2 diabetes (1). Further, both Roux-en-Y gastric bypass and sleeve gastrectomy, the most frequently applied bariatric procedures worldwide, are associated with remission of type 2 diabetes, with a recent meta-analysis showing gastric bypass to have higher short-term remission rates as compared with sleeve gastrectomy (2).

Type 2 diabetes is characterized by insufficient secretion of insulin from the pancreatic  $\beta$ -cells, coupled with impaired insulin action in target tissues. Both enhanced insulin secretion and insulin sensitivity contribute to improved glycemic control after bariatric surgery (3, 4). Despite seemingly higher remission rates of type 2 diabetes after gastric bypass vs sleeve gastrectomy (2), similar improvements in insulin secretion and  $\beta$ -cell function have been reported after the 2 procedures in patients with type 2 diabetes and obesity (5-9). In accordance with these findings, previously published data from the Oseberg study showed similar beneficial effects of the surgical procedures on  $\beta$ -cell function as assessed by an intravenous glucose tolerance test (10).

While intravenously administered glucose addresses the intrinsic regulation of insulin secretion, oral tests also measure extrinsic regulation by activating the entero-insular axis (11). Nutrient intake stimulates or inhibits the secretion of a number of gastrointestinal hormones, including glucagon-like peptide-1 (GLP-1), glucose-dependent insulintropic polypeptide (GIP), glucagon, and ghrelin (11). Insulin secretion is amplified when glucose is taken orally (as opposed to infused intravenously) (12). This phenomenon is known as the incretin effect and is conveyed by the 2 incretin hormones GLP-1 and GIP. People with type 2 diabetes have an impaired incretin effect, most likely due to an impaired  $\beta$ -cell response to the incretin hormones (13, 14).

Altered gastrointestinal hormone responses after bariatric surgery are believed to mediate some of the beneficial effects of bariatric surgery on glucose homeostasis. Studies comparing the 2 surgical procedures have shown different results varying from higher nutrient-stimulated GLP-1 levels after gastric bypass (7, 8) and lower ghrelin levels after sleeve gastrectomy (7), to no between-group differences in GLP-1 (5, 6), GIP (5, 7, 8), glucagon (5, 6) and ghrelin levels (6). How these combined hormone responses influence insulin secretion in type 2 diabetes after bariatric surgery is not yet fully understood.

In summary, it remains unclear whether changes in postprandial gastrointestinal hormones and  $\beta$ -cell function differ between gastric bypass and sleeve gastrectomy. We aimed to explore potential differences between the surgical procedures in gastrointestinal hormones and  $\beta$ -cell function after glucose ingestion. We hypothesized that when compared with sleeve gastrectomy, gastric bypass would be associated with higher oral glucose tolerance test (OGTT)-derived GLP-1 levels and greater  $\beta$ -cell response to glucose 1 year after surgery.

## Methods

### Trial Design

The Oseberg study is an ongoing randomized, triple-blind, single-center, parallel group trial taking place at a tertiary care obesity center at Vestfold Hospital Trust, Norway. Patients with severe obesity and type 2 diabetes were randomized and underwent either Roux-en-Y gastric bypass or sleeve gastrectomy. The primary outcomes, 1-year remission of diabetes (glycated hemoglobin [HbA1c]  $\leq 42$  mmol/mol [6.0%] without antidiabetic medication) and  $\beta$ -cell function measured by an intravenous glucose tolerance

test, have been published (10). All participants provided written informed consent. The study was approved by the Regional Committees for Medical and Health Research Ethics in Norway (ref: 2012/1427/REK sør-øst) and is in accordance with Helsinki-II declaration. The full protocol is published and available online (10).

## Participants

All patients scheduled for bariatric surgery were screened for study eligibility. Inclusion criteria were age  $\geq 18$  years, current body mass index (BMI)  $\geq 33.0$  kg/m<sup>2</sup> with previously verified BMI  $\geq 35.0$  kg/m<sup>2</sup>, and type 2 diabetes; HbA1c  $\geq 48$  mmol/mol (6.5%) or use of antidiabetic medications with HbA1c  $\geq 43$  mmol/mol (6.1%). Key exclusion criteria were major abdominal surgery, cancer, and severe endocrine, heart, lung, liver, or gastro-esophageal reflux disease (15).

## Randomization and Masking

Randomization and masking procedures have been described previously (10, 15). Patients were randomly allocated (1:1) to gastric bypass or sleeve gastrectomy by a computerized random number generator with a block size of 10. Sequentially numbered, sealed opaque envelopes were used to conceal allocation, which was revealed in the operating theater by the bariatric surgeon on the day of surgery. All study personnel, patients, and the primary outcome assessor were blinded to allocations. The surgeons did not participate in patient follow-up.

## Procedures

The 2 intervention groups received identical preoperative and postoperative treatment, including a low-calorie diet (< 1200 kcal per day) during the 2 weeks preceding surgery. Surgical procedures have been described previously (10, 15).

To monitor insulin secretion, an OGTT was performed on 2 separate days at baseline, 5 weeks, and 1 year after surgery. The participants were not allowed to eat, drink more than 2 dL of water, or smoke for 8 hours prior to the tests. Moreover, long acting GLP-1 analogues and other antidiabetic medications were terminated 6 weeks and 48 hours prior to the glucose tolerance tests, respectively. A cannula was inserted into a cubital vein and the cannulated arm wrapped in a heat pad throughout the experiment for the collection of arterialized blood samples during the glucose tolerance tests. For reasons of patient

safety, the upper limit of fasting blood glucose prior to the OGTT was set to < 25 mmol/L. The first patient experienced serious dumping symptoms after a 75 g oral glucose load (200 mL water) at the 5-week follow-up. The glucose load was therefore, after discussion within the steering committee, reduced to 25 g glucose (67 mL water) from April 8, 2013, onward. To estimate gastric emptying rate, a 1 g paracetamol tablet was crushed to powder, dissolved in the ready-to-use glucose solution, and ingested by the participants over 5 minutes. Blood samples were drawn before (–5 and 0 minutes) and after the combined glucose and paracetamol load at 15, 30, 60, 90, 120, and 180 minutes.

## Laboratory Analyses

Whole-blood HbA1c was analyzed on a Tosoh high-performance liquid chromatography G8 analyzer (Tosoh Corporation, Tokyo, Japan). During the OGTT, at all time points, blood was collected in: (i) one tube and centrifuged after 30 minutes. The serum was set on ice and stored at –80 °C until the analysis of insulin (RRID: AB\_2756877) and C-peptide (RRID:AB\_2893132); (ii) one tube containing lithium heparin and centrifuged immediately before the analysis of plasma glucose and paracetamol the same day; and (iii) one chilled tube containing EDTA for the analysis of GLP-1, GIP, ghrelin, and glucagon. The tubes were immediately centrifuged at 4 °C before plasma was separated from cells and put on ice and stored at –80 C. Plasma glucose and paracetamol were analyzed on Vitros 5.1 (Ortho-Clinical Diagnostics, Raritan, New Jersey, USA) until October 2017 and on a Cobas 8000 analyzer (Roche Diagnostics, Mannheim, Germany) thereafter. Serum C-peptide and insulin were analyzed on a Cobas 6000 and a Cobas e601 analyzer, respectively. Before measurement of GLP-1, GIP and glucagon samples were extracted in a final concentration of 70% ethanol. Total GLP-1 and GIP concentrations were measured using radioimmunoassays specific for the C-terminal of the GLP-1 (antibody code no 89390; RRID:AB\_2892195) and GIP molecules (code no. 80867; RRID:AB\_2892194) respectively. For glucagon, a C-terminally directed antiserum (code no. 4305; RRID:AB\_2892837) measuring glucagon of pancreatic origin was used. Sensitivity for all assays was below 1 pmol/L, and the intra-assay coefficient of variation below 10%. Total ghrelin was measured using Millipore Human Ghrelin Elisa (cat no EZGRT-89K, Millipore, USA; RRID:AB\_2892838) and carried out in accordance with the manufacturer's instructions. All quality controls were within accepted limits.

## Outcomes

Prespecified secondary outcomes from the Oseberg study included in the present analysis were first, OGTT-derived measures of insulin secretion; second, fasting and oral glucose-stimulated levels of glucose, insulin, C-peptide, and gastrointestinal hormones; and third, gastric emptying rate as assessed by an oral paracetamol test (15). All prespecified secondary outcomes were assessed 3 weeks before surgery, and 5 weeks and 1 year after surgery.

## Calculations

Incremental area under the curve (iAUC) was calculated using the trapezoidal rule by subtracting fasting levels from total AUC derived from the OGTT. Due to the biphasic rise-and-fall pattern of glucagon with levels both above and below fasting values, iAUC glucagon was divided into an early (iAUC<sub>0-60</sub>) and a late period (iAUC<sub>60-180</sub>). For all the other variables, iAUC<sub>0-180</sub> were calculated. Maximal paracetamol concentration (C<sub>max</sub>), time to peak paracetamol concentration (T<sub>max</sub>) and iAUC paracetamol were used as markers of gastric emptying rate and gastrointestinal absorption.

Prehepatic insulin secretion rate (ISR) (pmol/kg/min) was calculated from C-peptide concentrations by deconvolution, using ISEC software program (16) (with settings: Subjects with obesity, Coefficient of Variation 5%, and basal function on). The following set of assumptions were adopted for calculating prehepatic insulin secretion rate: (i) C-peptide kinetics were described by a 2-compartment model; (ii) the parameters in the model of C-peptide kinetics were approximated from the subject's weight, height, age, sex, and classification (as Normal, Obese or NIDDM); (iii) the measurement errors were uncorrelated, normal with zero mean, and with a constant coefficient of variation.

We estimated  $\beta$ -cell glucose sensitivity ( $\beta$ -GS), a measure of OGTT-derived insulin secretion, as the dose response relationship between ascending post-OGTT glucose levels and ISR values. Time to peak glucose concentration was identified for each subject. ISR values were plotted against the corresponding glucose levels till the time to peak glucose in a cross-correlation analysis (17). The slope of this linear relationship represents  $\beta$ -GS (picomoles per kilograms per minute per millimolar) representing the change in ISR per millimolar increase in glucose.

Hepatic insulin clearance (HIC) was derived using ISR and insulin in the fasting state ( $HIC_{fasting} = \text{ISR}_{fasting} / \text{Insulin}_{fasting}$ ) and the postprandial state ( $HIC_{OGTT} = \text{iAUC}_{OGTT} \text{ Insulin}$ ) (18).

Symptoms of early (first hour during OGTT) and late dumping (1-3 hours during OGTT) were assessed and graded using Arts' dumping score (19). Symptomatic hypoglycemia was defined as having symptoms of hypoglycemia (late dumping score > 0) and a blood glucose concentration of 3.9 mmol/L or less at 60, 90, 120, or 180 minutes during OGTT.

## Statistical Analysis

Sample size was estimated for the primary outcomes of the study and is described elsewhere (15). Briefly, given a 5% significance level and 80% power, a total study sample of 110 subjects (remission) or 100 subjects (disposition index) was required to reveal a difference between groups. Given our study population of 106 patients, a probability of type-1 error ( $\alpha$ ) of 0.05, and a mean (SD)  $\beta$ -GS 1 year after gastric bypass of 1.7 (1.1) pmol/kg/min/mmol (approximated from (20)), our study had an 80% power to detect a 0.6 pmol/kg/min/mmol difference in  $\beta$ -GS between the 2 procedures. Per-protocol analyses were performed after the exclusion of subjects with missing 25-g OGTT.

Crude differences between the 2 groups for binary outcomes were analyzed using a Fisher exact test. Continuous outcomes were compared using independent samples *t* test, Mann-Whitney U test, as well as linear mixed models for repeated measures using unstructured covariance matrix (fixed effect: group, time, and group-time interaction; and random effect: patient). In case of significant interactions, post hoc analyses were performed to identify the nature of the interaction and between-group differences were reported. Statistical analyses were conducted using SPSS (version 25.0) and STATA (version 15.0).

Due to limited statistical power, we had to reduce the complexity of the mediation analysis and performed preliminary correlation analyses to assess potential mediators correlated with  $\beta$ -GS. The following variables were analyzed: GLP-1, GIP, glucagon, ghrelin (independents) and  $\beta$ -GS (dependent). Second, we regressed  $\beta$ -GS and remission of diabetes. Thereafter, mediation analyses were conducted using the PROCESS macro developed for SPSS by Hayes (21). The mediation model included operation group as exposure, remission as outcome, and mediators selected with the correlation analyses. We estimated the direct effect of operation on remission and specific indirect effects through the mediators.

## Results

Between Oct 15, 2012, and Sept 1, 2017, 319 consecutive patients with type 2 diabetes were assessed for eligibility; 210 patients were ineligible, excluded, declined

participation, or withdrew consent, leaving 109 patients to be randomly assigned to either gastric bypass or sleeve gastrectomy (Supplementary Fig. 1 (22)). A 25-g OGTT was performed in 99 patients at baseline, 99 patients at 5 weeks, and 96 patients at the 1-year follow-up time point (Supplementary Fig.1 (22)). A total of 106 patients (67% women) completed a 25-g OGTT at least once and were included in the analyses, with 53 patients in each group.

The patients had a mean (SD) age of 48 (10) years, BMI 42.0 (5.0) kg/m<sup>2</sup>, duration of diabetes 6.2 (5.6) years, and HbA1c of 65 (18) mmol/mol (8.1% [1.7%]). Among the 93 patients taking glucose lowering drugs, 21 patients used GLP-1 analogues and 21 were receiving insulin treatment. There were no differences between groups at baseline (Supplementary Table 1 (22)).

At the 1-year follow-up, mean body weight was significantly lower, and the partial and complete remission rates were significantly higher after gastric bypass (85% and 77%) than after sleeve gastrectomy (58% and 48%) (Table 1). Fasting glucose, HbA1c, and postchallenge glucose concentrations decreased similarly in both groups (Table 1, Fig. 1A). Incremental AUC<sub>0-180</sub> glucose was significantly lower at 5 weeks in the gastric bypass group but did not differ between groups at 1 year (Table 1). Fasting ISR dropped, and iAUC<sub>0-180</sub> ISR changed similarly in both groups (Table 1). However, ISR values at 15 and 30 minutes were significantly higher 1 year after gastric bypass than after sleeve gastrectomy (Fig. 1B). The OGTT trajectories of insulin and C-peptide levels mirrored the ISR trajectories (Supplementary Fig. 2 (22)).

β-GS increased by approximately 3-fold after sleeve gastrectomy and 4-fold after gastric bypass, and at 1 year, β-GS was 54% greater in the gastric bypass group (between-group difference 0.45 pmol/kg/min/mmol [95% CI, 0.15-0.75]; *P* = 0.0032) (Table 1, Fig. 2).

Fasting GLP-1 levels changed marginally and similarly in the 2 groups (Table 1). Conversely, iAUC<sub>0-180</sub> GLP-1 increased more after gastric bypass than after sleeve gastrectomy (4-fold vs 3-fold increase), and the mean 1-year iAUC<sub>0-180</sub> GLP-1 was 79% higher after gastric bypass (between-group difference 1173 pmol/L \* min [95% CI, 569-1776]; *P* = 0.0010) (Table 1). Furthermore, the 15- and 30-minute OGTT GLP-1 levels were approximately 2-fold higher 1 year after gastric bypass (Fig. 3A). Fasting GIP levels fell similarly in both groups (Table 1). However, iAUC<sub>0-180</sub> GIP increased significantly more after gastric bypass than after sleeve gastrectomy from baseline to 1 year (Table 1). Moreover, at 1 year, the gastric bypass group had slightly higher GIP levels 15 minutes after glucose ingestion (Fig. 3B). Fasting glucagon decreased significantly and similarly in both groups (Table 1). The OGTT-glucagon trajectory had a biphasic

rise-and-fall pattern with no significant difference in glucagon levels between the 2 procedures at any time (Fig. 3C). However, at 5 weeks and 1 year, iAUC<sub>0-60</sub> glucagon was significantly greater after gastric bypass than after sleeve gastrectomy at 5 weeks and 1 year (Table 1). Fasting ghrelin values decreased after sleeve gastrectomy and increased after gastric bypass (Table 1). Moreover, all ghrelin levels during OGTT were significantly higher after gastric bypass (Fig. 3D). However, the reduction in ghrelin levels (negative iAUC<sub>0-180</sub>) during the OGTT was significantly greater after gastric bypass than after sleeve gastrectomy (Table 1, Fig. 3D).

Time to peak paracetamol concentrations decreased, and C<sub>max</sub> paracetamol and iAUC<sub>0-180</sub> paracetamol increased significantly more after gastric bypass than after sleeve gastrectomy (Table 1, Fig. 3E).

Insulin clearance in the fasting state increased significantly more in the gastric bypass group than in the sleeve gastrectomy group, while postprandial insulin clearance remained unchanged in both groups (Table 1).

At 1 year, iAUC<sub>0-180</sub> GLP-1 was moderately correlated with β-GS (*r* = 0.37, *P* < 0.0001), while no significant correlations were shown between iAUC<sub>0-180</sub> GIP, iAUC<sub>0-60</sub> glucagon, iAUC<sub>0-180</sub> ghrelin, and β-GS (*r* = 0.07, *P* = 0.53; *r* = 0.04, *P* = 0.72; and *r* = -0.02, *P* = 0.83, respectively). Further, there was a significant association between β-GS and remission of diabetes (OR = 56 [95% CI, 10-308]; *P* < 0.0001). Operation group was significantly associated with iAUC<sub>0-180</sub> GLP-1, which was significantly associated with β-GS and remission (Supplementary Fig. 3 (22)). Given the model depicted in Supplementary Fig. 3 (22), the effect of type of operation was mediated through the indirect pathway: type of operation > iAUC<sub>0-180</sub> GLP-1 > β-GS > remission (OR = 2.8 [95% CI, 1.4-12.2]; *P* < 0.001).

At 1 year, C<sub>max</sub> paracetamol correlated with both iAUC<sub>0-180</sub> GLP-1 (*r* = 0.39, *P* < 0.001) and β-GS (*r* = 0.23, *P* = 0.03).

Early dumping symptoms during the OGTT were similar in both groups (Supplementary Table 2 (22)). After gastric bypass, symptomatic hypoglycemia was observed in 2 patients (4%) at 5 weeks and in 1 patient (2%) at 1 year.

## Discussion

Several lines of evidence indicate that gastric bypass induces rapid delivery of ingested nutrients to L-cells in the distal small intestine, leading to increased secretion of GLP-1 and increased β-cell response to glucose, followed by improved glucose tolerance (4). Although similar mechanisms may explain the beneficial effects of sleeve gastrectomy on glucose homeostasis in people with type 2 diabetes, the existing evidence is sparse, with only a few small studies having directly compared the 2 procedures (5-8).

**Table 1.** Glycemia,  $\beta$ -cell function, gastrointestinal hormones, paracetamol, and insulin clearance at baseline, 5 weeks, and 1 year

	Baseline			5 weeks			1 year			P value
	Sleeve gastrectomy (n = 53)	Gastric bypass (n = 53)		Sleeve gastrectomy (n = 53)	Gastric bypass (n = 53)		Sleeve gastrectomy (n = 53)	Gastric bypass (n = 53)		
<b>Glycemia</b>										
Fasting glucose, mmol/L	12.4 (11.5, 13.3)	11.7 (10.8, 12.6)	..	7.9 (7.0, 8.8)	7.1 (6.2, 8.0)	..	7.2 (6.3, 8.1)	5.9 (5.0, 6.8)	..	<0.0001
iAUC <sub>0-180</sub> glucose, mmol/L × min	276 (235, 328)	311 (270, 352)	..	370 (328, 411)	289 (248, 330)**	..	293 (251, 334)	271 (229, 313)	..	0.013
Time to peak glucose, minutes	55 (51, 59)	55 (51, 59)	..	39 (35, 43)	39 (35, 43)	..	35 (31, 39)	29 (25, 33)	..	<0.0001
HbA1c, %	8.3 (8.0, 8.7)	7.9 (7.5, 8.2)	..	6.7 (6.4, 7.0)	6.4 (6.1, 6.8)	..	6.2 (5.8, 6.5)	5.8 (5.5, 6.2)	..	<0.0001
Diabetes medication, n (%)	48 (91)	45 (85)	..	32 (62)	26 (49)	..	19 (37)	7 (13)**	..	NA
Remission, n (%)	0 (0)	0 (0)	..	12 (23)	9 (17)	..	25 (48)	40 (77)**	..	NA
Body weight - kg	125 (120, 131)	124 (119, 130)	..	110 (105, 116)	110 (104, 115)	..	97 (92, 103)	89 (83, 94)**	..	<0.0001
Weight loss, %	0 (0)	0 (0)	..	12 (10, 13)	12 (10, 13)	..	23 (22, 24)	29 (28, 30)**	..	<0.0001
<b>Beta-cell function</b>										
Fasting ISR, pmol/kg/min	3.7 (3.4, 4.0)	3.9 (3.6, 4.1)	..	3.1 (2.9, 3.4)	3.2 (2.9, 3.5)	..	2.6 (2.3, 2.8)	2.4 (2.1, 2.7)	..	<0.0001
iAUC <sub>0-180</sub> ISR, pmol/kg/min	150 (107, 194)	158 (114, 201)	..	322 (278, 366)	366 (322, 410)	..	248 (205, 292)	315 (270, 360)	..	<0.0001
$\beta$ -GS, pmol/kg/min	0.30 (0.11, 0.50)	0.32 (0.12, 0.51)	..	1.04 (0.85, 1.24)	1.19 (1.00, 1.39)	..	0.85 (0.66, 1.04)	1.31 (1.12, 1.51)**	..	<0.0001
<b>Gastrointestinal hormones</b>										
Fasting GLP-1, pmol/L	10.6 (9.2, 12.1)	10.9 (9.4, 12.3)	..	9.3 (7.9, 10.8)	9.7 (8.2, 11.1)	..	11.8 (10.3, 13.2)	12.7 (11.2, 14.2)	..	0.0001
iAUC <sub>0-180</sub> GLP-1, pmol/L × min	535 (173, 896)	728 (370, 1086)	..	1532 (1174, 1890)	2692 (2337, 3047)**	..	1736 (1375, 2097)	3102 (2737, 3467)**	..	<0.0001
Fasting GIP, pmol/L	16.1 (14.4, 17.8)	16.9 (15.2, 18.6)	..	14.7 (12.9, 16.4)	12.3 (10.6, 14.0)	..	14.2 (12.4, 15.9)	12.5 (10.7, 14.3)	..	<0.0001
iAUC <sub>0-180</sub> GIP, pmol/L × min	2021 (1743, 2298)	1744 (1467, 2022)	..	2713 (2438, 2988)	2524 (2251, 2797)	..	2081 (1808, 2353)	2362 (2081, 2642)	..	<0.0001
Fasting Glucagon, pmol/L	20.4 (17.8, 22.9)	23.9 (21.3, 26.4)	..	14.3 (11.8, 16.9)	15.8 (13.2, 18.4)	..	12.1 (9.6, 14.7)	12.6 (10.0, 15.3)	..	<0.0001
iAUC <sub>0-60</sub> Glucagon, pmol/L × min	-42 (-104, 20)	-4 (-65, 57)	..	-0.44 (-61, 60)	171 (110, 233)**	..	-112 (-173, -52)	13 (-49, 75)**	..	<0.0001
iAUC <sub>60-180</sub> Glucagon, pmol/L × min	-323 (-408, -238)	-335 (-421, -249)	..	-90 (-176, -3.2)	-196 (-281, -112)	..	101 (16, 187)	78 (-8, 165)	..	<0.0001
Fasting Ghrelin, pg/mL	241 (209, 272)	188 (157, 220)	..	86 (53, 117)	179 (147, 210)**	..	87 (55, 119)	269 (236, 301)**	..	<0.0001
iAUC <sub>0-180</sub> Ghrelin, pg/mL × min	-8146 (-9867, -6424)	-7648 (-9346, -5950)	..	-4016 (-6624, -3209)	-8599 (-10297, -6902)**	..	-5227 (-6935, -3519)	-10454 (-12193, -8714)**	..	0.0009
<b>Paracetamol</b>										
	..	..	..	..	..	..	..	..	..	..

**Table 1. Continued**

	Baseline		5 weeks		1 year		P value		
	Sleeve gastrectomy (n = 53)	Gastric bypass (n = 53)	Sleeve gastrectomy (n = 53)	Gastric bypass (n = 53)	Sleeve gastrectomy (n = 53)	Gastric bypass (n = 53)	Group	Time	
C <sub>max</sub> paracetamol, mmol/L	66 (57, 74)	69 (61, 77)	87 (79, 96)	142 (134, 151)**	90 (82, 99)	150 (142, 159)**	<0.0001	<0.0001	<0.0001
T <sub>max</sub> paracetamol, minutes	50 (46, 54)	54 (50, 59)	34 (30, 39)	17 (13, 21)**	32 (28, 36)	15 (11, 20)**	<0.0001	<0.0001	<0.0001
iAUC <sub>0-180</sub> Paracetamol, mmol/L × min	6635 (5917, 7353)	7070 (6366, 7774)	8897 (8174, 9620)	10476 (9768, 11185)**	8759 (8043, 9474)	10393 (9677, 11109)**	0.0109	<0.0001	0.0002
<b>Insulin clearance</b>	..	..	..	..	..	..	..	..	..
Fasting insulin clearance, L/min/kg	0.023 (0.020, 0.027)	0.021 (0.018, 0.025)	0.031 (0.027, 0.035)	0.035 (0.031, 0.039)	0.040 (0.037, 0.044)	0.051 (0.047, 0.055)**	0.042	<0.0001	0.0002
Postprandial insulin clearance, L/min/kg	0.03 (-0.07, 0.13)	-0.03 (-0.13, 0.07)	0.07 (-0.03, 0.17)	0.04 (-0.06, 0.15)	0.08 (-0.2, 0.18)	0.11 (0.004, 0.22)	0.65	0.182	0.68

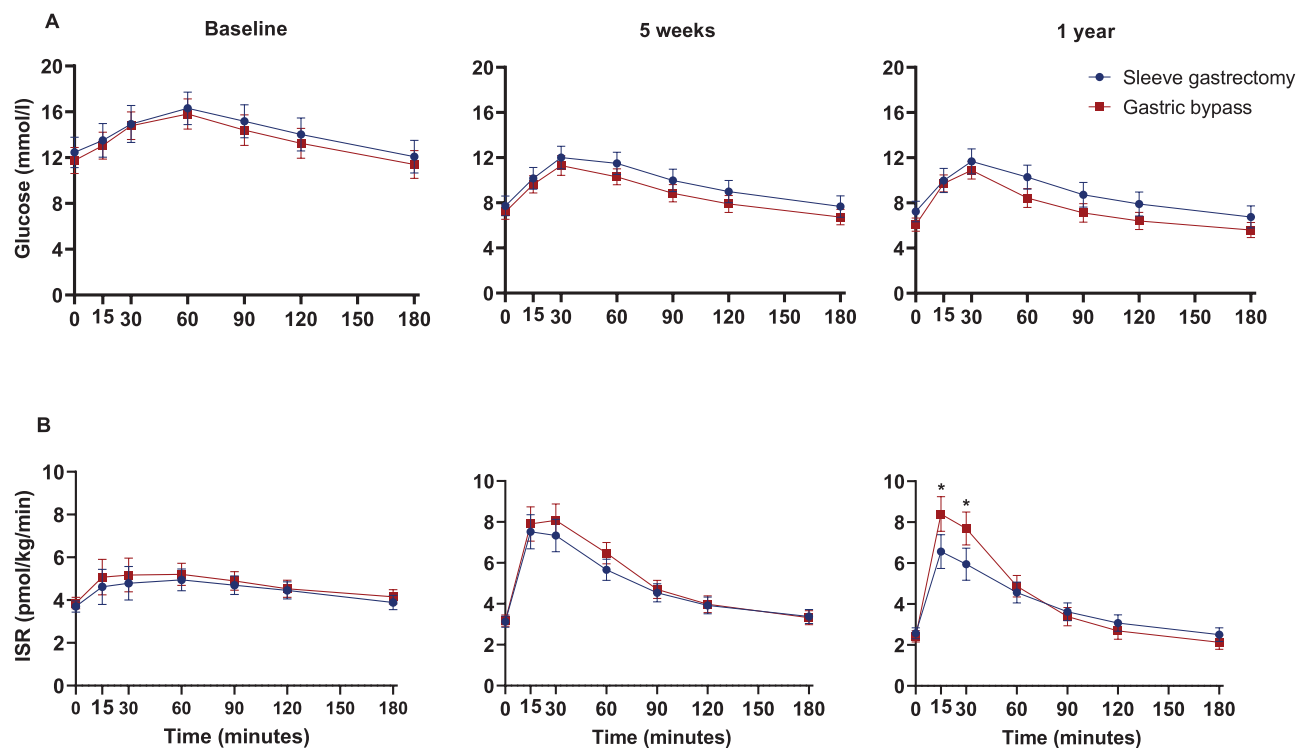
Outcome variables are reported as mean (95% CI) for continuous variables (linear mixed models) or crude numbers (%) for categorical variables (Fisher exact test). \*  $P < 0.05$ , \*\*  $P < 0.01$  between-group difference. Abbreviations: β-GS, Beta-cell glucose sensitivity; peak concentration; GIP, glucose-dependent insulintropic polypeptide; GLP-1, glucagon-like peptide-1; iAUC, incremental area under the curve; ISR, insulin secretion rate; T<sub>max</sub>, time to peak concentration.

The main novel findings of the present randomized controlled study of patients with type 2 diabetes were that, compared with sleeve gastrectomy, gastric bypass was associated with significantly greater improvement in OGTT-derived β-cell function and higher postchallenge GLP-1 levels. These findings add to the understanding of the observed differences in remission rates of type 2 diabetes between these bariatric procedures.

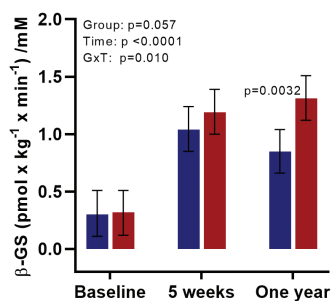
The mechanisms explaining lower glucose levels in patients with type 2 diabetes after sleeve gastrectomy and gastric bypass overlap in part. Caloric restriction after the operations greatly improves hepatic insulin sensitivity and glycemia, as reported previously (10). Thereafter, weight loss improves peripheral insulin sensitivity, which in turn further improves glycemia. This common chain of beneficial effects may reduce the toxic effect of glucose on insulin-producing cells, as indicated by similar improvements in first-phase insulin secretion after sleeve gastrectomy and gastric bypass (10). By contrast, in the present substudy of the Oseberg trial, insulin secretion assessed after an oral glucose load with activation of the entero-insular axis, was significantly greater 1 year after gastric bypass than after sleeve gastrectomy. Collectively, these findings indicate that insulin hypersecretion after gastric bypass is linked to the oral, but not the intravenous, route of glucose administration.

Contrasting with our findings, 4 previously published studies showed similar insulin secretion after the surgical procedures after an oral nutrient load in patients with obesity and type 2 diabetes (5-8). However, the oral nutrient stimuli and the assessment of insulin secretion differed between these studies, making direct comparisons difficult. In addition, the previous studies might have been underpowered (sample sizes < 37 participants), resulting in false negative results. Finally, 3 of the 4 studies were nonrandomized and subject to selection bias.

The incretin effect corresponds positively with the oral glucose load (13). Despite using a small 25 g glucose load, we document higher postchallenge GLP-1 levels after gastric bypass than after sleeve gastrectomy as reported by the authors of 2 small studies (7, 8), albeit not by others (5, 6). Moreover, a correlation between increased β-cell function and higher GLP-1 secretion after surgery, as observed in this study, has been reported previously (6, 23). The effect on GLP-1 and insulin secretion would probably have been greater if the glucose load had been higher. Moreover, we found a statistical association between GLP-1 secretion, β-GS, and diabetes remission. However, since the present study was not designed to study any underlying mechanisms, we can only speculate that enhanced GLP-1 secretion and improved β-cell function may have contributed to diabetes remission.



**Figure 1.** Glucose (A) and prehepatic insulin secretion rates-ISR (B) during oral glucose tolerance tests in patients undergoing sleeve gastrectomy and gastric bypass at baseline, 5 weeks, and 1 year. Plots are mean and 95% CI from linear mixed effects models for repeated measures, \* $P < 0.01$  for between-group difference reported for time points showing significant group  $\times$  time interaction.



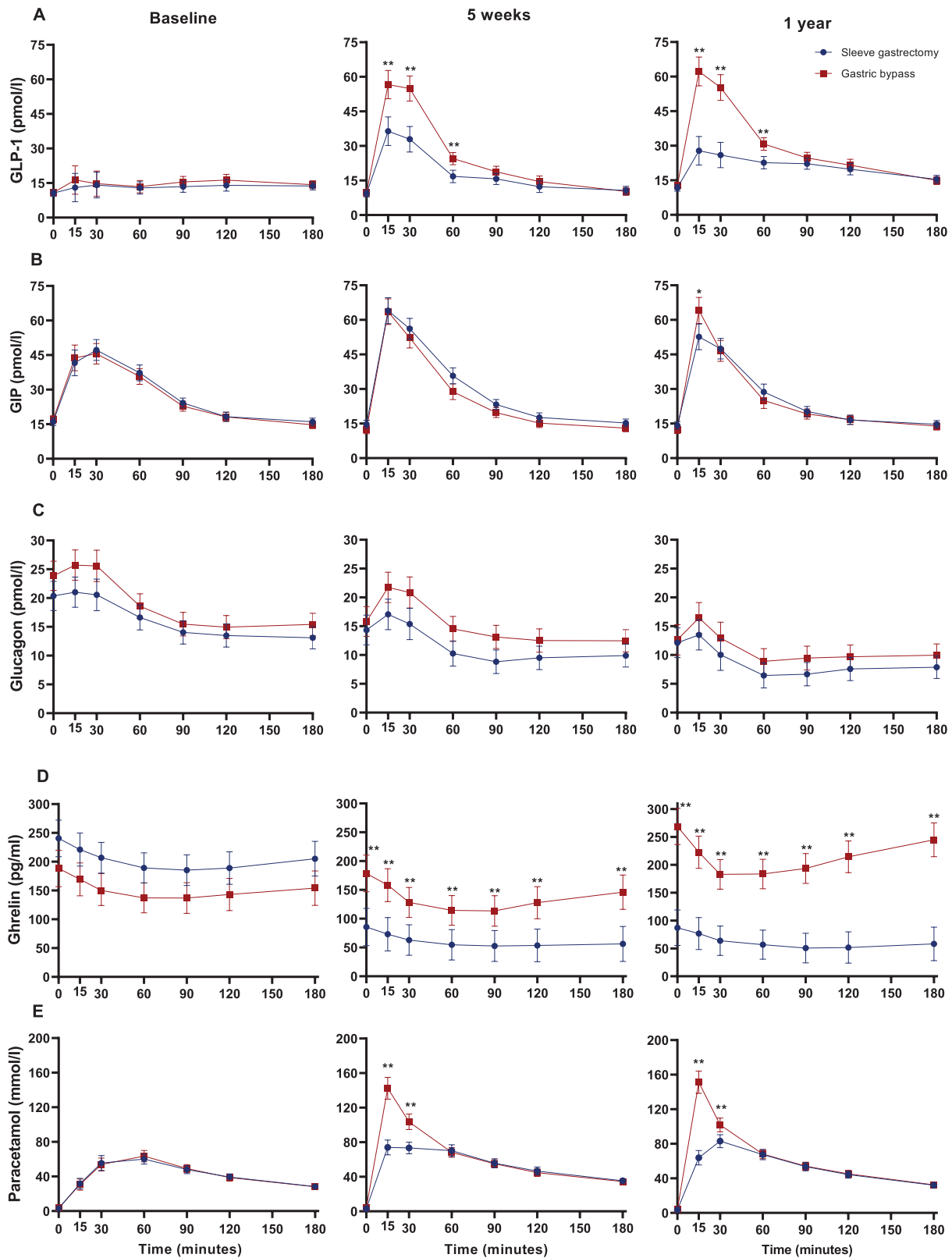
**Figure 2.** Beta-cell glucose sensitivity ( $\beta$ -GS), mean and 95% CI from linear mixed effects models for repeated measures assessed by oral glucose tolerance tests at baseline, 5 weeks, and 1 year after sleeve gastrectomy (blue bars) and gastric bypass (red bars).

Importantly, results from experimental studies show that blocking of the GLP-1 receptor 1 week to 3 months after gastric bypass increased postchallenge glucose concentrations and impaired  $\beta$ -cell response to oral glucose in patients with type 2 diabetes (24, 25). The findings in this study support the idea of the aforementioned mechanism, suggesting an important role of GLP-1 secretion on postsurgical glucose control. Whether this is solely due to enhanced GLP-1 secretion after surgery is unknown. Reversal of  $\beta$ -cell resistance to GLP-1 could also contribute to increased  $\beta$ -cell response to glucose. However, there are diverging results in this respect.

Preserved insulinotropic action of GLP-1 has been observed 3 months after gastric bypass surgery in patients with normal glucose tolerance (26). Partly contrasting with this finding, reduced  $\beta$ -cell sensitivity to GLP-1 has been reported in patients with normal glucose tolerance after gastric bypass compared with matched controls (27).

In contrast with previous reports including patients with obesity and type 2 diabetes, we found greater GIP and glucagon response to an oral nutrient stimulus after gastric bypass and sleeve gastrectomy (5-8). There were no correlations between these hormones and  $\beta$ -GS. Although both GIP and glucagon may influence insulin secretion (11), our findings do not support a major impact of these hormones on  $\beta$ -cell function after these procedures. As observed in previous studies, sleeve gastrectomy reduced ghrelin levels dramatically (6, 7). Lower ghrelin levels after sleeve gastrectomy are a result of resection of the gastric fundus. Although ghrelin may inhibit glucose-stimulated insulin secretion (28), we did not find any significant correlation between changes in ghrelin levels during OGTT and  $\beta$ -GS.

In accordance with previous reports, paracetamol absorption was enhanced after both procedures, although to a greater extent after gastric bypass (25, 29). Moreover, maximal paracetamol levels correlated positively with both GLP-1 secretion and  $\beta$ -GS. These findings indicate that the



**Figure 3.** Gastrointestinal hormones: glucagon-like peptide-1 (GLP-1) (A), glucose-dependent insulintropic polypeptide (GIP) (B), glucagon (C), ghrelin (D), and paracetamol (E) concentrations during oral glucose tolerance tests in patients undergoing sleeve gastrectomy and gastric bypass at baseline, 5 weeks, and 1 year. Plots are mean and 95% CI from linear mixed effects models for repeated measures, \* $P < 0.01$  and \*\* $P < 0.001$  for between-group difference reported for time points showing significant group  $\times$  time interaction.

increase in circulating GLP-1 and improvement in  $\beta$ -cell function after surgery may partly be explained by a more rapid passage of nutrients into the intestine.

Surprisingly, as compared with sleeve gastrectomy, the significantly greater improvement in OGTT-derived  $\beta$ -cell function after gastric bypass did not translate into lower postchallenge glucose levels at 1 year. This apparent lack of difference between procedures may be due to the relatively low glucose load administered and/or insufficient power. However, our findings are in keeping with the studies assessing postchallenge glucose levels after the 2 procedures (5-8).

Our study is strengthened by its randomized design and the inclusion of a larger population than in previous studies enabling unbiased assessment of effect size and an increase in power to reveal previously undocumented differences between the 2 procedures. However, the study has some limitations. First, the results were based on secondary outcomes of the Oseberg study, which increases the risk of both false positive and false negative results. Second, the generalizability of the results is limited by the single-center design, the inclusion of largely white participants and a relatively short 1-year follow-up period. Third, the study was not designed to address any underlying mechanisms for remission of type 2 diabetes.

The role of GLP-1 in diabetes remission after bariatric surgery has been debated for several years. The regulation of insulin secretion is complex and factors such as several nutrients and hormones (30), not addressed in this paper, are likely to influence  $\beta$ -cell function after bariatric surgery. Nevertheless, our results support the assumption of enhanced GLP-1-potentiated insulin secretion as a contributor to improved glycemic control after sleeve gastrectomy and gastric bypass (30). These findings add to our understanding of the observed differences in remission rates of type 2 diabetes between gastric bypass and sleeve gastrectomy and may therefore help patients and health personnel during the shared decision process over treatment choice.

## Acknowledgments

We thank the participants, the patient representative, and the study personnel. We particularly thank Linda Mathisen, Karina Bautz, Berit Mossing Bjørkås, Andreas Aarvik, Heidi Omre Fon, Hanna Lakso, and Astrid Hillestad (Morbid Obesity Centre, Vestfold Hospital Trust, Tønsberg, Norway) for their continuous efforts, enthusiasm, and patient care, thereby ensuring the collection of high-quality data in the Oseberg study. We also thank Matthew McGee (Morbid Obesity Centre, Vestfold Hospital Trust) for proofreading the manuscript.

ISEC is a software program developed by Roman Hovorka, PhD, Metabolic Modelling Group, Centre for Measurement and Information in Medicine, Department of Systems Science, City University, Northampton Square, London EC1V OHB, United Kingdom. ISEC is available, at no charge, to interested investigators.

**Financial Support:** The funder of the study (the Morbid Obesity Centre, Vestfold Hospital Trust, Tønsberg, Norway) had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.

**Author Contributions:** D.H. and J.H. conceived the study and are the principal investigators. D.H., F.F., K.I.B., H.L.G., J.K.H., M.S., R.S., J.J.H., and J.H. contributed to the design and oversaw the study conduct. J.J.H. and B.H. generated data and contributed to the framing of research questions and interpretation of the results. D.H., F.F., and J.H. wrote the first version of the manuscript. M.C.S. was responsible for the statistical analyses. All authors critically participated in interpretation of the data, reviewed the manuscript for intellectual content and approved the final version of the manuscript. Four authors (D.H., F.F., M.C.S., and J.H.) had independent access to the complete data set. All authors took responsibility for data completeness and accuracy, as well as the fidelity of the trial to the protocol. The first, second (corresponding) and last authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Prior Presentation:** Parts of this study were presented as an oral presentation at the 80th Scientific Sessions of the American Diabetes Association (ADA), Virtual, June 12-16, 2020.

**Clinical Trial Information:** ClinicalTrials.gov registration no. NCT01778738.

## Additional Information

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**Disclosures:** F.F. declares an educational grant (PhD) from South-Eastern Norway Regional Health Authority during the study period. J.H. declares honoraria from Novo Nordisk and Boehringer Ingelheim, outside the submitted work. K.I.B. declares grants from Novo Nordisk, Lilly, Merck, Astra Zeneca, Boehringer Ingelheim, and Roche Diagnostics, outside the submitted work. H.L.G. declares other financial relationships from Novo Nordisk, GlaxoSmithKline, and Astra Zeneca, outside the submitted work. M.S. declares honoraria from Boehringer Ingelheim, outside the submitted work. J.J.H. is a member of advisory boards for NovoNordisk. D.H. declares honoraria from Novo Nordisk, Lilly, and Sanofi, outside the submitted work. The other authors declare no conflicts of interest.

**Data Availability:** Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. Access to data collected from this study, including anonymized individual participant data, will be made available following publication upon email request to the corresponding author. Data will be shared with investigators whose proposed use of the data has been approved by the Oseberg steering committee and is in accordance with the consent given by the participants as well as Norwegian law and legislation.

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