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# GLP-1 and GIP may play a role in long-term weight trajectories after gastric bypass

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**Introduction:** Suboptimal clinical responses to metabolic and bariatric surgery include insufficient weight loss (WL), weight regain (WR), and/or comorbidity remission failure or relapse. Gut hormones' role in WR and Type 2 diabetes (T2D) relapse is not fully established. So, our aim was to evaluate the hormone profiles of patients with long-term optimal and suboptimal response after gastric bypass (RYGB).

**Methods:** This cross-sectional study included 43 individuals who underwent RYGB surgery over 10 years ago, divided into two groups: 23 participants with no T2D history but different WR trajectories (cohort 1), and 20 with prior T2D diagnosis and optimal WL (cohort 2), with post-RYGB T2D remission (n=10) or relapse (n=10).

**Results:** Fasting and postprandial glucose, insulin, C-peptide, glucagon, GLP-1 and GIP levels were evaluated during a mixed-meal tolerance test. In cohort 1, fasting glucose, insulin, C-peptide, and glucagon, as well as the postprandial glucose and GIP levels, were significantly positively correlated with %WR. Additionally, postprandial GLP-1 and glucagon levels were negatively correlated with the %WR. In cohort 2, higher postprandial glucose and lower insulin were observed in participants with T2D relapse. No other significant differences were observed.

**Discussion:** In sum, greater WR was associated with higher levels of postprandial glucose and GIP, along with lower GLP-1 and glucagon excursions. Whether these are cause or consequence of WR remains to be clarified. Additionally, GIP and GLP-1 profile of participants with T2D relapse did not differ from those with T2D remission.

## KEYWORDS

RYGB, suboptimal long-term outcomes, weight regain, T2D relapse, enteropancreatic hormones

## 1 Introduction

While Roux-en-Y gastric bypass (RYGB) leads to substantial and sustained weight loss (WL) in the majority of individuals, along with significant improvements or even resolution of obesity-related conditions, especially type 2 diabetes (T2D) (1), approximately 20–30% experience suboptimal clinical response within 10 years (1–3). These suboptimal outcomes include insufficient total weight loss (TWL <20% at 12 months), weight regain (WR) after initial weight nadir, and/or recurrence of T2D following an initial remission (4).

Although the mechanistic aspects of metabolic bariatric surgery (MBS), consisting in gastric volume restriction and intestinal malabsorption, were initially thought to be the only culprits for the observed response to MBS, it is long known that they are just part of the equation. Gut hormones also play a crucial role, as evidenced by the rapid normalization of blood glucose in individuals with T2D shortly after MBS, even before significant WL occurs (5, 6). Indeed, the mechanical modifications of the gastrointestinal tract in RYGB result in the earlier delivery of nutrients to the distal intestine that stimulate local neuro-endocrine cell populations, responsible for the secretion of several gut-derived hormones, such as Glucagon-like Peptide 1 (GLP-1) and Peptide YY (PYY), which contribute to increased satiety and improved glycemic control (7, 8). In fact, GLP-1 paramount role in mediating the effects of RYGB is now well established (5), and GLP-1 receptor agonists are used for obesity and diabetes treatment (9, 10). In contrast, the putative role of the other incretin hormone, Glucose-dependent Insulinotropic Polypeptide (GIP) in mediating the effects of MBS is much less clear given the disparities found in GIP levels after MBS and conflicting results from both human and animal studies (11). Therefore, it has been assumed that if there was any GIP contribution for MBS outcomes, it was likely to be negligible. Still, in non-operated euglycemic individuals, GIP seems to have a more important role in  $\beta$ -cell function than GLP-1 (5). Moreover, there is evidence that the two hormones have comparable activity after sleeve gastrectomy whereas GLP-1 stands out as predominant after RYGB (5), even though, the incretin effect of endogenous GIP is weak or absent in people with T2D (12). More recently, tirzepatide, a GLP-1 receptor and GIP receptor (GIPR) co-agonist, demonstrated greater WL and antidiabetic efficacy compared to isolated GLP-1 receptor (GLP-1R) agonists (13), GIP was brought back into the spotlight and elicited a renewed interest in further understanding its role in glucose and energy homeostasis (14, 15).

While MBS efficacy has been widely investigated, the reasons for a suboptimal clinical response, in particular whether gut hormones also play a role in WR or T2D relapse is less well established (8). Therefore, the aim of this study was to gain further insights into the putative mechanisms leading to MBS suboptimal response through the evaluation of hormone profiles of individuals with optimal and suboptimal response to MBS due to WR or T2D relapse.

## 2 Materials and methods

### 2.1 Participant selection

The study participants were identified from our retrospective cohort study that evaluated WL and comorbidity remission at 10 or more years after RYGB surgery (3, 16). A sub-set of these patients (N=43) were invited, accepted and gave their informed consent to join this study, which comprised two separate cohorts with different inclusion criteria.

#### 2.1.1 Cohort 1 – Analysis of hormone profiles of individuals with different weight trajectories (n=23)

To focus on weight trajectories analysis, we defined the inclusion criteria as individuals with no history of T2D who achieved optimal WL - defined as a TWL greater than 20% within two years after surgery. Exclusion criteria comprised individuals who had short- or long-term surgical complications or who were under drugs with glucose-lowering and/or obesity management medications.

Participants among this cohort included individuals who were able to sustain the WL and other individuals who experienced a suboptimal clinical response over the long term.

Given that there is lack of consensus on criteria for WR after a successful initial WL in patients submitted to MBS, participants were not grouped according to WL response. Instead, the %TWL and the percentage of WR after nadir were evaluated as continuous variables and correlated with the entero-pancreatic dynamics described below.

#### 2.1.2 Cohort 2 - Analysis of hormone profiles of individuals with sustained T2D remission vs T2D relapse (n=20)

To focus on T2D relapse analysis, we defined the inclusion criteria for this cohort as individuals diagnosed with T2D prior undergoing MBS with optimal WL over the long-term after surgery. Participants with short- or long-term surgical complications were excluded.

Participants were divided into two groups: participants who experienced either sustained T2D remission [HbA1c < 6.4% and FPG < 7.0 mmol/L without any antidiabetic medication for at least 3 months after surgery (17), (n=10)] or people with T2D relapse after remission (n=10), despite optimal WL over the long-term after surgery. These participants were matched by pre-operative age, pre-operative body mass index (BMI) and time since surgery. The participants were not taking drugs with glucose-lowering and/or weight-loss potential, except for the ones with T2D relapse, who were on metformin only.

This separate analysis of two different cohorts was designed to allow the identification of hormonal profiles related to WL trajectories and to T2D relapse, without co-interference.

The study was approved by the institutional ethical review board (approval numbers: CA-0172/19-0t\_MP/AC and CA-149/2020-0t\_MP/AC). All procedures performed were in accordance with the ethical standards of the institutional and national research committee and complied with the 1964 Helsinki declaration and its later amendments. Data are protected according to GDPR policies in place.

## 2.2 Surgical procedures

All surgeries were performed at a single bariatric surgery center, by the same team of general surgeons, using a standard laparoscopic RYGB technique with a fixed 120-cm alimentary limb and a differing biliopancreatic limb length: between 60 cm and 90 cm for the classical procedure or 200cm for the metabolic variant, as previously described (18). Participants were submitted to either surgical technique in a non-random assignment over 10 years earlier, according to the subjects' anatomical and clinical features. Participants with no past medical history of T2D underwent a RYGB with a biliopancreatic limb length up to 90 cm long (classic RYGB), while participants with T2D diagnosed prior to surgery and optimal WL after RYGB who experienced either sustained T2D remission or T2D relapse, there was a balanced proportion of patients either submitted to classic (80% and 60%, respectively) or long (20% and 40%, respectively) biliopancreatic limb RYGB.

## 2.3 Mixed meal tolerance test

Participants underwent a mixed meal tolerance test (MMTT) following a 12 hour overnight fast. In addition, participants on metformin (cohort 2: participants with T2D relapse) took their last dose at least 12 hours before the MMTT.

Participants ingested a standardized commercially available liquid meal (Fresubin Energy Drink, 200 mL, 300 kcal [50E% carbohydrate, 15E% protein and 35E% fat]; Fresenius Kabi Deutschland, Bad Homburg, Germany) over a maximum period of 15 minutes. Venous blood samples were collected into EDTA tubes (S-Monovette® 7.5 mL, K2 EDTA Gel, 1.6 mg/mL, Sarstedt), before the meal (−15 and 0 min) and at 15, 30, 45, 60, 90, and 120 min after the start of meal intake. The plasma was then separated and stored at −20°C until assayed.

## 2.4 Biochemical measurements

Blood glucose was measured at every timepoint of the MMTT using a glucometer (Freestyle Precision Neo Glucose meter, Abbott, USA). Insulin and C-peptide levels were measured by an electrochemiluminescence sandwich immunoassay (ECLIA) on Atellica® (Siemens), as previously described (19). The lower detection limits for insulin and C-peptide were 4.8 pmol/L and

36.4 pmol/L, respectively. Inter- and intra-assay coefficients of variation were below 5%.

For GIP, GLP-1 and glucagon measurements, plasma samples were extracted using 70% ethanol. Total GLP-1, total GIP, and glucagon levels were measured using validated in-house radioimmunoassays (RIA) targeted to the C-terminal of GLP-1 (antiserum 89390), GIP (antiserum 867) and glucagon (antiserum 4305) (20). The lower detection limits for GLP-1 and GIP were 5 pmol/L, and 2.5 pmol/L for glucagon. Average inter- and intra-assay coefficients of variation were below 15%.

## 2.5 Calculations and statistical analysis

The % TWL [(preoperative weight – weight at MMTT) ÷ (preoperative weight) × 100], and the %WR [(weight at MMTT – nadir weight) ÷ (nadir weight) × 100] were determined.

HOMA Calculator version 2.2.4 (<http://www.dtu.ox.ac.uk>, accessed November 2023) was used to determine the updated homeostasis model assessment indexes (HOMA2) as surrogate measures of beta cell function (HOMA2-B), peripheral insulin sensitivity (HOMA2-S) and resistance (HOMA2-IR).

Total and incremental areas under the curve (tAUC and iAUC, respectively) were calculated using the trapezoidal rule, without and with subtraction of the fasting hormonal levels from the subsequent timepoints, respectively. The fasting values were assumed as the mean value of the two fasting samples. The insulinogenic index (IGI) was calculated as the ratio of the incremental C-peptide from fasting to 30 minutes during the MMTT to glucose changes within the same period. The oral glucose insulin sensitivity (OGIS) was assessed and then multiplied by IGI to compute the Disposition Index, which targets insulin secretion corrected for insulin sensitivity. Insulin secretion rate (ISR) was determined by deconvolution from C-peptide plasma levels (CV 5%) with correction for age, sex and BMI using the ISEC program (ISEC, Version 3.4a, Hovorka, 1994). Finally, insulin clearance was calculated as the ratio between tAUC of the ISR and the tAUC of insulin.

Since participants in Cohorts 1 and 2 exhibited distinct pre- and post-operative characteristics, and the study aims to separately assess outcomes related to WL and T2D remission/relapse, no statistical comparisons were made between the two cohorts. So, all the statistical analyses were performed within each cohort. Nominal variables were expressed as number of cases and percentage (%), and the continuous variables are expressed as mean ± standard deviation (SD), unless stated otherwise. Missing data was handled by complete-case analysis, excluding participants with missing data for the variables analyzed. For nominal variables, the Fisher's exact test was used. Continuous variables that did not meet the assumption of normality (Cohort 2: follow-up time; T2D duration; HbA1c at MMTT; fasting glucose; insulin clearance; IGI, disposition index; ISR iAUC; C-peptide tAUC; insulin iAUC and tAUC; GLP-1 tAUC) were analyzed using the Mann-Whitney

test. The remaining variables met the normality assumption and were analyzed using unpaired two-tailed t-tests. Comparisons between timepoints during the MMTT were performed using a two-way analysis of variance (ANOVA) with Sidak's *post hoc* test, for cohort 2. Linear regression was performed to assess the predictive value of preoperative age, weight and BMI for %TWL and %WR 10 years after surgery.

WR and TWL correlation with glucose and hormonal profiles were evaluated using the Pearson correlation test. A *post hoc* power analysis for sample size was performed for these correlations, with our primary hypothesis being that postprandial GLP-1 levels would be inversely correlated with %WR. This hypothesis was based on the well-established effect of GLP-1 on WL following RYGB (21). A power of 80.8% was achieved with a sample size of  $n = 23$  using a one-sided test (as an inverse correlation was hypothesized), with an  $r$ -value cutoff of -0.50 and a significance level of  $p < 0.05$ .

Statistical analyses were performed using the GraphPad Prism version 10.1.1 and the IBM SPSS statistics software version 20.0.0.0. A  $p < 0.05$  was considered statistically significant.

## 3 Results

### 3.1 Anthropometric and glycemic status trajectories after RYGB surgery

Study participants' characteristics before RYGB and at MMTT are presented in Table 1. In the cohort with no history of T2D (Cohort 1), the %TWL since surgery up to MMTT ranged between 0% and 43.22% while %WR after nadir ranged from 0% to 47.06% (Supplementary Figure 1). Using linear regression, we found that pre-operative BMI significantly predicted the %TWL after surgery ( $\beta = -1.71$  [95% CI -2.95; -0.46],  $p = 0.009$ ) and the %WR after nadir ( $\beta = 6.02$  [95% CI 1.47; 10.6],  $p = 0.012$ ) (Supplementary Table 1).

Participants with T2D before RYGB (Cohort 2) experienced remission in the first post-operative year, with the sole exception of one participant (who underwent T2D remission 5 years after RYGB). Among those who relapsed, this was observed 7.22  $\pm$  4.18 years after surgery. No significant differences in post-operative body weight, BMI and %TWL at time of evaluation

TABLE 1 Anthropometric and glycemic status trajectories after RYGB.

|                                     | Cohort 1: no prior T2D | Cohort 2: pre-operative T2D |                       |              |
|-------------------------------------|------------------------|-----------------------------|-----------------------|--------------|
|                                     |                        | Remission                   | Relapse               | p            |
| N                                   | 23                     | 10                          | 10                    | —            |
| Sex, m:f (%)                        | 4:19<br>(17.4%:82.61%) | 1:9<br>(10.0%:90.0%)        | 0/10<br>(0.0%:100.0%) | >0.999       |
| Type of RYGB, classic:metabolic (%) | 0:23<br>(0.0%:100.0%)  | 8:2<br>(80.0%:20.0%)        | 6:4<br>(60.0%:40.0%)  | 0.629        |
| <b>Pre-operative</b>                |                        |                             |                       |              |
| Age (years)                         | 34.13 $\pm$ 6.06       | 47.10 $\pm$ 8.74            | 49.40 $\pm$ 5.74      | 0.495        |
| Body weight (kg)                    | 120.20 $\pm$ 13.56     | 113.5 $\pm$ 12.1            | 105.3 $\pm$ 14.8      | 0.192        |
| BMI (kg/m <sup>2</sup> )            | 45.36 $\pm$ 3.68       | 45.38 $\pm$ 5.31            | 42.96 $\pm$ 5.04      | 0.309        |
| <b>Post-operative</b>               |                        |                             |                       |              |
| Age (years)                         | 48.35 $\pm$ 6.29       | 62.10 $\pm$ 7.98            | 62.90 $\pm$ 5.90      | 0.802        |
| Body weight (kg)                    | 93.39 $\pm$ 21.75      | 77.0 $\pm$ 8.9              | 72.4 $\pm$ 11.1       | 0.320        |
| BMI (kg/m <sup>2</sup> )            | 35.22 $\pm$ 7.26       | 30.85 $\pm$ 4.40            | 29.61 $\pm$ 4.57      | 0.544        |
| Time since surgery (years)          | 12.30 $\pm$ 1.02       | 13.00 $\pm$ 1.41            | 12.80 $\pm$ 0.92      | 0.739        |
| Body weight nadir (kg)              | 76.91 $\pm$ 13.64      | 72.10 $\pm$ 8.10            | 69.55 $\pm$ 10.5      | 0.552        |
| TWL nadir (%)                       | 36.25 $\pm$ 5.87       | 36.35 $\pm$ 5.13            | 33.89 $\pm$ 4.62      | 0.274        |
| TWL MMTT (%)                        | 22.84 $\pm$ 11.87      | 31.98 $\pm$ 5.93            | 31.03 $\pm$ 7.18      | 0.750        |
| WR (%)                              | 20.91 $\pm$ 2.92       | 8.43 $\pm$ 7.22             | 6.37 $\pm$ 6.02       | 0.496        |
| T2D duration before RYGB (years)    | NA                     | 3.25 $\pm$ 3.77             | 5.00 $\pm$ 2.60       | 0.067        |
| FPG MMTT (mg/dl)                    | 77.00 $\pm$ 3.70       | 80.50 $\pm$ 14.76           | 130.10 $\pm$ 40.10    | <b>0.005</b> |
| HbA1c MMTT (%)                      | 5.30 $\pm$ 0.28        | 5.58 $\pm$ 0.33             | 6.91 $\pm$ 0.93       | <b>0.002</b> |

Data is presented as mean  $\pm$  standard deviation (SD). T2D type 2 diabetes, RYGB Roux-en-Y gastric bypass, BMI body mass index, TWL total weight loss, MMTT mixed meal tolerance test, NA Not applicable, WR weight regain, FPG fasting plasma glucose, HbA1c glycated hemoglobin. Only the groups within Cohort 2 were compared. Unpaired t-test or Mann-Whitney test (depending on the variables normality): statistically significant differences ( $p < 0.05$ ) are highlighted in bold.

were observed when participant subgroups with sustained T2D remission vs relapse were compared nor correlated with pre-operative BMI (Table 1). Before surgery, none of the patients were under insulin therapy. However, patients with T2D relapse had higher HbA1c levels ( $5.47 \pm 0.43$  vs  $7.08 \pm 0.63$ ,  $p=0.045$ ) and longer T2D duration before RYBG ( $3.25 \pm 3.77$  vs  $5.00 \pm 2.60$ ,  $p=0.067$ ).

3.2 Glucose, insulin and C-peptide profiles

In participants without previous history of T2D (Cohort 1), fasting glucose, insulin, and C-peptide levels, along with insulin resistance (HOMA2-IR), were negatively correlated with %TWL. In contrast, insulin sensitivity (HOMA2-S and OGIS) and the disposition index were positively correlated with %TWL (Figure 1). The opposite correlations were observed when these were analyzed against the %WR (Figure 1).

In the cohort of participants with T2D prior to RYGB, significantly greater postprandial glucose (tAUC  $1123.0 \pm 260.6$  vs  $829.4 \pm 165.0$  mmol/L x min,  $p= 0.008$ ) (Table 2; Figure 2) and lower insulin (tAUC  $30911 \pm 13770$  vs  $59580 \pm 26382$  pmol/L x min,  $p=0.005$ ) excursions were observed in the T2D relapse subgroup (vs remission), but no significant differences in C-peptide excursion profiles were observed between subgroups (Table 2). IGI was also lower in the subgroup with T2D relapse vs T2D remission (IGI:  $0.7 \pm 0.5$  vs  $1.9 \pm 1.6$ ,  $p=0.009$ ) (Table 2). Moreover, significantly lower HOMA2-B ( $48.7 \pm 25.3\%$  vs  $78.4 \pm 20.3\%$ ,  $p=0.010$ ) and OGIS ( $352.6 \pm 69.4$  vs  $417.8 \pm 35.9$ ,  $p=0.017$ ) were found in the T2D relapse subgroup as compared to the T2D

remission one, while insulin clearance was significantly higher ( $0.020 \pm 0.01$  vs  $0.014 \pm 0.01$ ,  $p=0.024$ ) (Table 2).

3.3 GLP-1, GIP and glucagon dynamics

In participants without a history of T2D, fasting GLP-1, postprandial GLP-1, and postprandial glucagon levels were positively correlated with %TWL after surgery, while postprandial GIP levels were negatively correlated with %TWL. In contrast, postprandial GLP-1 and glucagon levels were negatively correlated with %WR, whereas postprandial GIP levels and fasting glucagon levels were positively correlated with %WR (Figure 3).

Comparing the subgroups of individuals with T2D prior to surgery, no significant differences in fasting or postprandial excursion of GIP, GLP-1 and glucagon were observed (Figure 2; Table 3).

4 Discussion

This study shows that long-term WR after RYGB is associated with elevated fasting glucose, insulin resistance, and a blunted postprandial GLP-1 response alongside an exaggerated GIP response. On the other hand, T2D relapse correlates with impaired insulin secretion but not with altered incretin dynamics.

In particular, although the participants have no medical history of T2D, the patients with higher %WR have higher fasting levels of glucose, insulin, C-peptide and insulin resistance, as well as lower insulin sensitivity. The significant correlation between the %WR

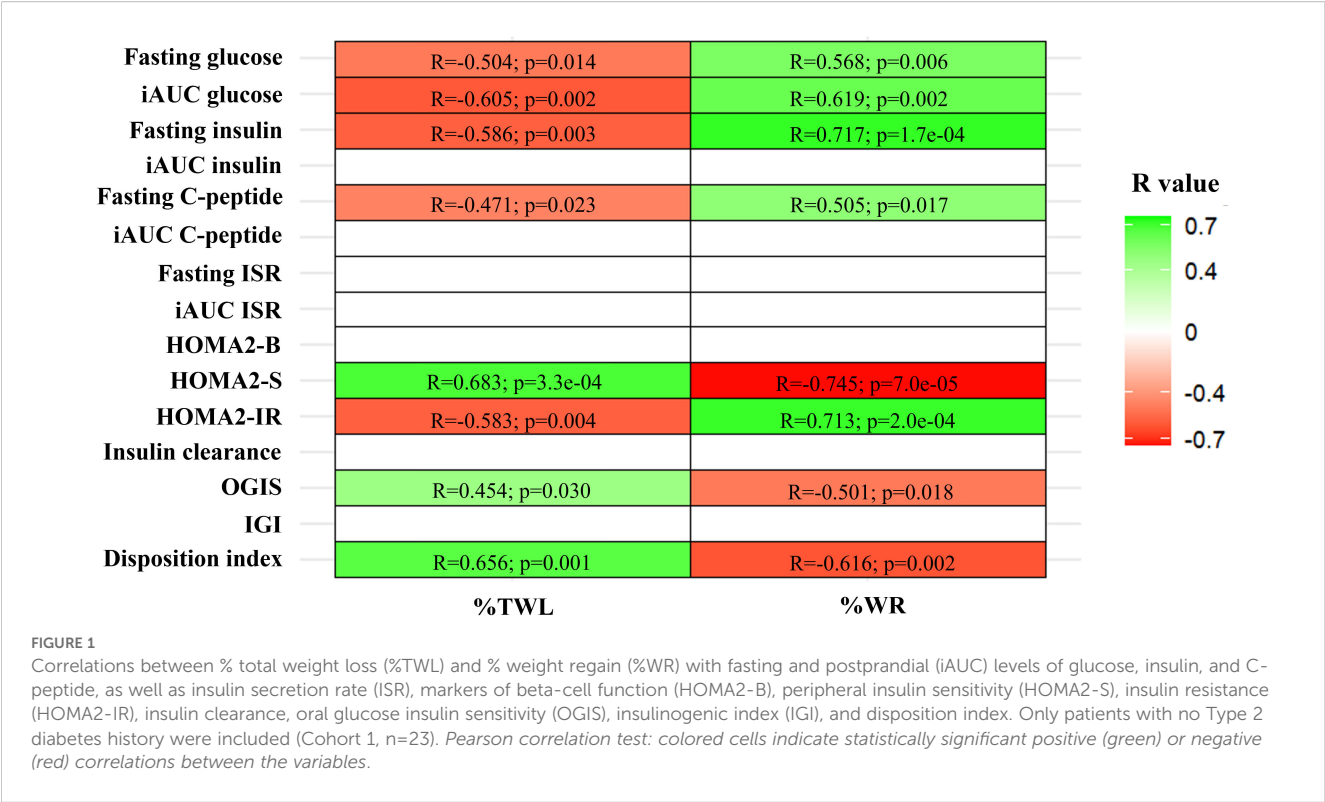


TABLE 2 Glucose, insulin, C-peptide dynamics, as well as insulin secretion rates and sensitivity after RYGB.

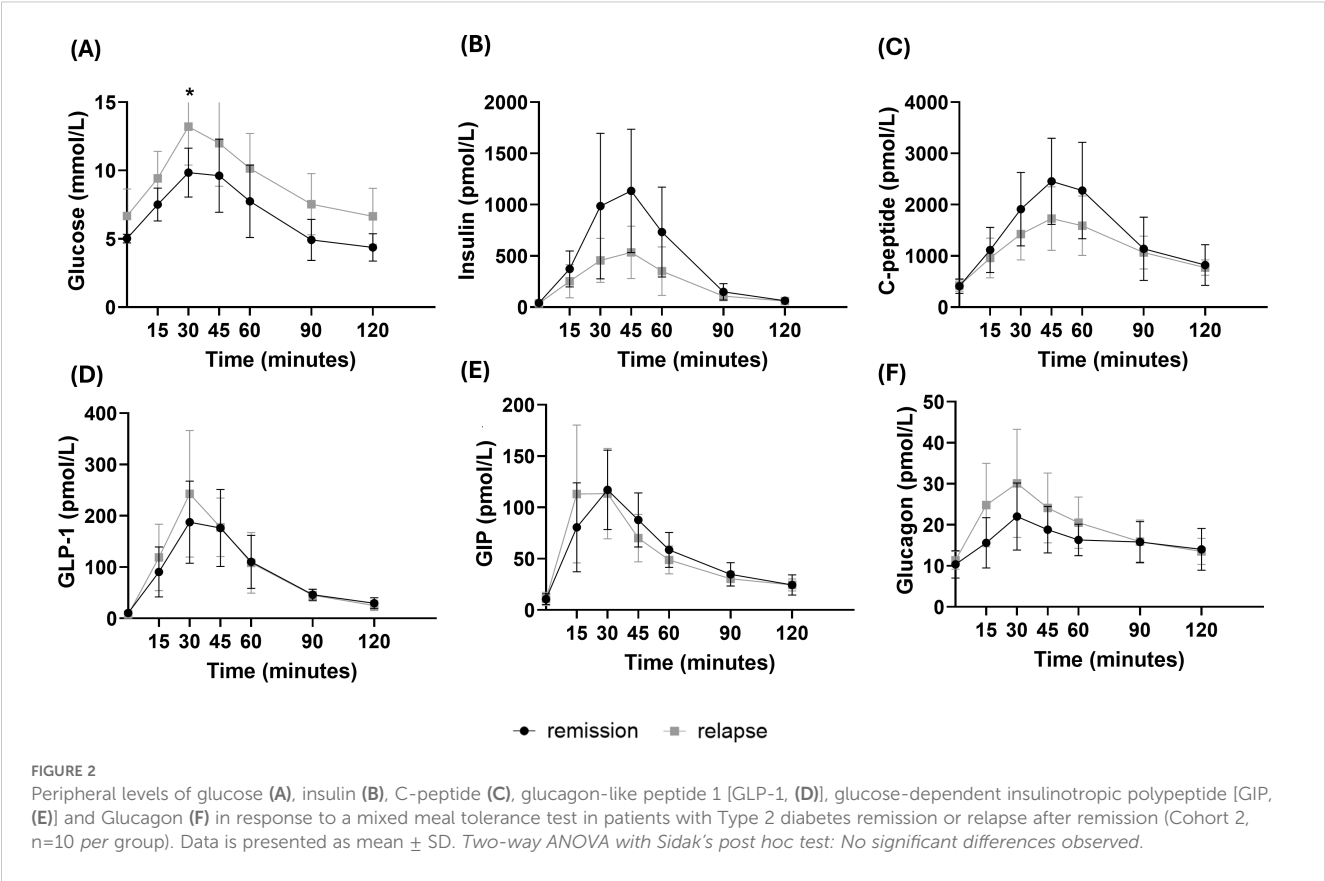
|                           | Cohort 1: no prior T2D | Cohort2: pre-operative T2D |                |              |
|---------------------------|------------------------|----------------------------|----------------|--------------|
|                           |                        | remission                  | relapse        | p            |
| Glucose                   |                        |                            |                |              |
| Fasting (mmol/L)          | 4.91 ± 0.83            | 5.02 ± 0.31                | 6.67 ± 1.98    | <b>0.005</b> |
| iAUC (mmol/L x min)       | 202.27 ± 70.10         | 279.7 ± 113.5              | 341.2 ± 140.9  | 0.297        |
| tAUC (mmol/L x min)       | 714.59 ± 199.37        | 829.4± 165.0               | 1123.0 ± 260.6 | <b>0.008</b> |
| Insulin                   |                        |                            |                |              |
| Fasting (pmol/L)          | 44 ± 34                | 40 ± 12                    | 35 ± 12        | 0.378        |
| iAUC (pmol/L x min)       | 34430 ± 13474          | 54741 ± 25762              | 26661 ± 13198  | <b>0.007</b> |
| tAUC (pmol/L x min)       | 39747 ± 14854          | 59580 ± 26382              | 30911± 13770   | <b>0.005</b> |
| C-peptide                 |                        |                            |                |              |
| Fasting (pmol/L)          | 265 ± 119              | 408 ± 140                  | 422 ± 110      | 0.819        |
| iAUC (pmol/L x min)       | 52521 ± 7340           | 133904 ± 53403             | 93445 ± 36457  | 0.063        |
| tAUC (pmol/L x min)       | 83867 ± 9368           | 182972 ± 65951             | 144085 ± 13432 | 0.248        |
| ISR                       |                        |                            |                |              |
| Fasting [pmol/(kg x min)] | 0.7 ± 0.31             | 1.2 ± 0.4                  | 1.3 ± 0.4      | 0.537        |
| iAUC                      | 199.0 ± 140.2          | 549.6 ± 232.6              | 397.1 ± 168.2  | 0.110        |
| tAUC                      | 259.3 ± 168.1          | 684.5 ± 276.4              | 555.6 ± 188.0  | 0.238        |
| IGI                       | 2.4 ± 2.0              | 1.9 ± 1.6                  | 0.7 ± 0.5      | <b>0.009</b> |
| Disposition Index         | 0.012 ± 0.012          | 0.009 ± 0.012              | 0.002 ± 0.004  | 0.132        |
| HOMA2-B (%)               | 82.4 ± 21.5            | 78.4 ± 20.3                | 48.7 ± 25.3    | <b>0.010</b> |
| HOMA2-IR                  | 0.8 ± 0.7              | 0.8 ± 0.2                  | 0.7 ± 0.2      | 0.579        |
| HOMA2-S (%)               | 160.9 ± 70.6           | 143.9 ± 46.9               | 157.5 ± 51.4   | 0.542        |
| OGIS                      | 428.5 ± 63.5           | 417.8 ± 35.9               | 352.6 ± 69.4   | <b>0.017</b> |
| Insulin Clearance         | 0.006 ± 0.003          | 0.014 ± 0.01               | 0.020 ± 0.01   | <b>0.024</b> |

Data is presented as mean ± SD. T2D type 2 diabetes, iAUC incremental area under the curve, tAUC total area under the curve, IGI insulinogenic index, HOMA2-B homeostasis model assessment for β-cell function, HOMA2-IR homeostasis model assessment for insulin resistance, HOMA2-S homeostasis model assessment for insulin sensitivity, OGIS oral glucose insulin sensitivity. Only the groups within Cohort 2 were compared. *Unpaired t-test or Mann-Whitney test (depending on the variables normality): statistically significant differences (p<0.05) are highlighted in bold.*

with glucose postprandial excursion but not with insulin/C-peptide postprandial profiles suggests that individuals with higher %WR face an additional challenge to control glucose levels after meals, unsurprisingly given the well-known association of obesity with increased risk of dysglycemia (22). Nonetheless, when corrected for insulin sensitivity (through calculation of the disposition index), there is an impairment of insulin secretion is those with more significant WR/lesser WL, which might possibly suggestive of beta-cell exhaustion, while perfect aligning with the documented relative lack of GLP-1 and glucagon postprandially, both of which known to be powerful insulinotropic hormones (23, 24).

We found significantly higher glucose and lower insulin excursions in the T2D relapse subgroup when compared to the T2D remission subgroup. Furthermore, lower HOMA2-B, OGIS and IGI were present in the T2D relapse subgroup. All together, these support the hypothesis of β-cell exhaustion at the end road of

insulin resistance, consistent with the pathological mechanisms underlying T2D (25, 26). In addition, a significantly higher insulin clearance was observed in patients with T2D relapse compared to patients with T2D remission. This could be explained by the fact that when T2D relapses, as a consequence of inadequate insulin secretion, there is a rise in glucose levels in the bloodstream. In the presence of normal insulin sensitivity, this could lead to the upregulation of insulin receptor expression primarily in the liver, responsible for the majority of the uptake of insulin and therefore its clearance. Indeed, this phenomenon of increased insulin clearance has been previously reported in patients with early onset T2D diabetes and normal insulin sensitivity (27). When focusing on hormone profiles, participants with higher % of WR present lower levels of fasting and postprandial levels of GLP-1. One of the key mechanisms contributing to successful initial WL following bariatric surgery is GLP-1 mediated. Previous studies



have consistently demonstrated that postprandial GLP-1 levels rise after RYGB (28) and that patients who experience greater WL after MBS have higher levels of GLP-1 compared to those with suboptimal WL (8, 29–32). In addition, and in line with our results, higher postprandial GLP-1 levels have also been observed in individuals with sustained WL, compared to those who experienced WR (32, 33). However, these results were not consistently confirmed by all studies reporting long-term

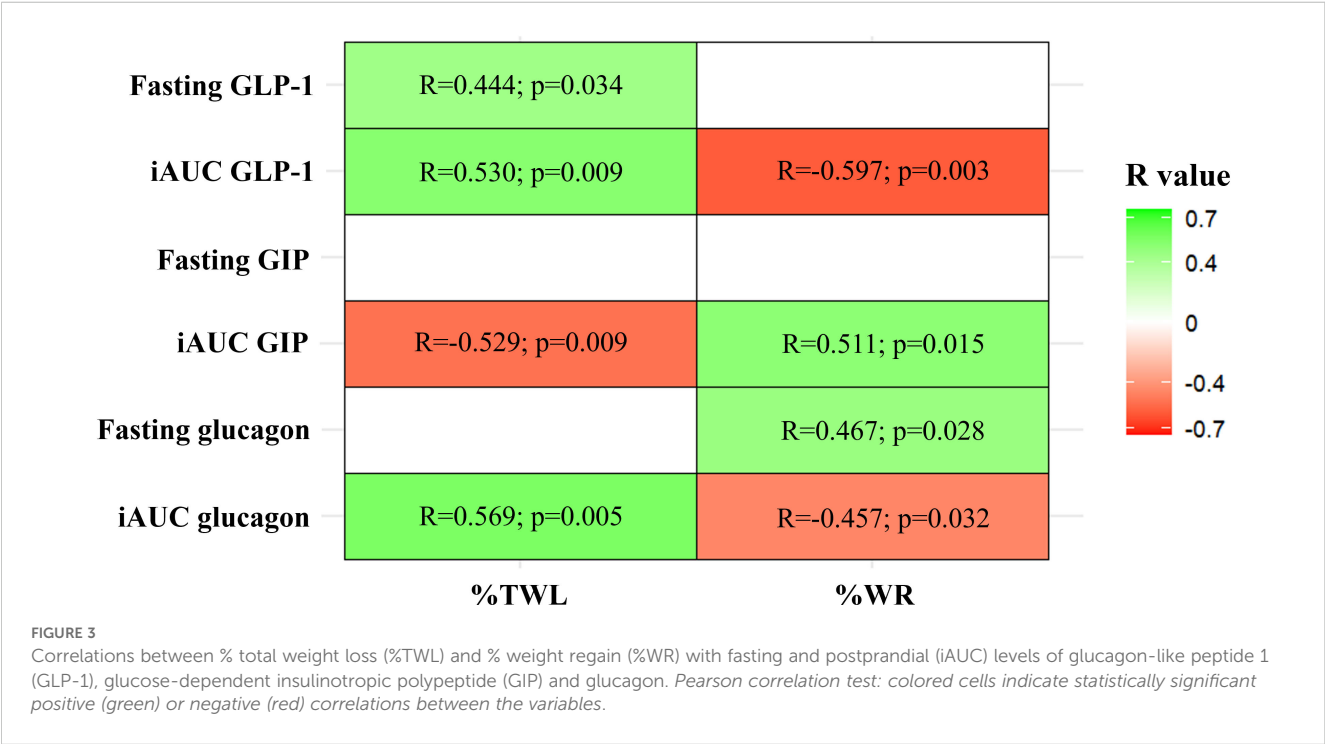


TABLE 3 Glucagon, GLP-1 and GIP dynamics after RYGB.

|                     | Cohort 1: no prior T2D | Cohort 2: pre-operative T2D |              | p     |
|---------------------|------------------------|-----------------------------|--------------|-------|
|                     |                        | Remission                   | Relapse      |       |
| Glucagon            |                        |                             |              |       |
| Fasting (pmol/L)    | 10 ± 4                 | 10 ± 3                      | 11 ± 2       | 0.436 |
| iAUC (pmol/L x min) | 577 ± 263              | 720 ± 286                   | 1058 ± 667   | 0.158 |
| tAUC (pmol/L x min) | 1687 ± 369             | 1962 ± 585                  | 2411 ± 728   | 0.145 |
| GLP-1               |                        |                             |              |       |
| Fasting (pmol/L)    | 9 ± 5                  | 10 ± 8                      | 7 ± 4        | 0.294 |
| iAUC (pmol/L x min) | 5979 ± 2168            | 9993 ± 3489                 | 11421 ± 4399 | 0.432 |
| tAUC (pmol/L x min) | 7020 ± 2365            | 11195 ± 3797                | 12309 ± 4340 | 0.529 |
| GIP                 |                        |                             |              |       |
| Fasting (pmol/L)    | 11 ± 7                 | 11 ± 5                      | 11 ± 7       | 0.912 |
| iAUC (pmol/L x min) | 4997 ± 1798            | 5858 ± 644                  | 5626 ± 744   | 0.817 |
| tAUC (pmol/L x min) | 6284 ± 1930            | 7088 ± 1790                 | 6903 ± 2430  | 0.848 |

Data is presented as mean ± SD. T2D type 2 diabetes, iAUC incremental area under the curve, tAUC total area under the curve, GLP-1 glucagon-like peptide-1, GIP glucose-dependent insulinotropic polypeptide. Only the groups within Cohort 2 were compared. *Unpaired t-test or Mann-Whitney test (depending on the variables normality): statistically significant differences ( $p < 0.05$ ) are highlighted in bold.*

outcomes. In particular, Lompropoulos et al. compared patients with successful WL maintenance and patients with WR 7 years post-surgery and found no significant differences in post-prandial GLP-1 levels (34).

In contrast to GLP-1 postprandial levels, which have been consistently reported to increase after RYGB, reports regarding the circulating levels of GIP following MBS are fewer and results have been inconsistent (28). Gao et al., in a meta-analysis, showed that changes in fasting GIP levels after RYGB are influenced by diabetes status. Specifically, individuals with T2D tended to show a more marked reduction in fasting GIP levels compared to those without T2D. In contrast, studies conducted in populations including both individuals with and without T2D often did not observe significant changes (35). In addition, short-term WL was not a significant predictor of fasting GIP reduction after RYGB (35). Sima E et al. also reported comparable levels of GIP during an oral glucose tolerance test between patients with and without optimal WL five years post-RYGB. On the other hand, Santo M et al. with a follow-up ranging from 27 to 59 months found that postprandial GIP levels were significantly different in patients with WR compared to those who experienced optimal WL maintenance (31, 32). The present study demonstrates that participants with greater WR after RYGB have higher GIP excursion following the intake of a mixed meal, despite having similar baseline levels. Nevertheless, it remains unclear whether these altered incretin dynamics are a cause or consequence of WR. It is possible that impaired GLP-1 signaling reduces satiety, leading to increased caloric intake and subsequent WR, while higher GIP levels may exacerbate this effect by promoting fat deposition (36, 37). Alternatively, WR itself might induce changes in incretin secretion. Both fasting and postprandial GLP-1 levels are lower in individuals with obesity compared to normal-weight (38), while

GIP levels have been reported to be higher in people with obesity in both basal (39) and stimulated states (40). Therefore, the results related to GIP and GLP-1 excursion observed in our study could be simply explained by the differences in BMI between the groups. Noteworthy is the fact that, in our study, no significant correlations were observed between %WR and fasting GIP and GLP-1 levels, while it is the response to the mixed meal that is distinct, which suggests that the BMI is unlikely to be the sole reason for the differences observed. Diets with high fat content were also reported to elicit greater postprandial GIP excursions (41). However, in our study the meal tolerance test was performed with a standardized mixed meal and all subjects had exactly the same meal challenge.

The discrepancies in the results across studies regarding the relation between postprandial GIP and GLP-1 levels and WR may be attributed to differences in the criteria used to define suboptimal outcomes, as well as the inclusion of patients with T2D in some analyses. People with T2D are known to exhibit distinct gastrointestinal hormone profiles (42). To minimize this bias regarding weight trajectories, our study excluded participants with a history of T2D from the %WR analysis and defined TWL and WR as non-categorical continuous variables, without committing any artificial or arbitrary cut-offs. Additionally, the divergences that were observed may suggest the involvement of other mechanisms in long-term weight maintenance after MBS.

Individuals with higher %WR exhibited higher fasting glucagon levels, along with higher glucose and insulin levels, likely reflecting their impaired insulin sensitivity. However, a contrasting pattern emerged when analyzing postprandial glucagon levels, as patients with greater %WR showed lower postprandial glucagon levels. While glucagon had not previously been directly correlated with WR after MBS, previous studies suggested that glucagon may contribute to WL by suppression of appetite and activation of

energy expenditure and thermogenesis (43). The discrepancy between fasting and postprandial glucagon levels correlation with %WR can be explained by the complex regulation of glucagon secretion and action after MBS (44).

There was an upsurge of GIP focused research since the extended-release GLP-1R and GIPR co-agonist tirzepatide became available for T2D and obesity treatment (13). However, the mechanism by which weight reduction is achieved is not totally clear, nor to what extent is the agonism of the GIP receptor responsible for the observed results (45), particularly since the insulinotropic effect of GIP is known to be severely hampered in patients with T2D (12, 46).

More recently, the triple agonist of GLP-1, GIP, and glucagon receptors (GCGR), retatrutide, was also developed. Retatrutide has shown impressive WL results of up to 24.2% after 48 weeks of treatment (47), which appear to be even more substantial compared to tirzepatide, despite there are no head-to-head clinical trials comparing tirzepatide and retatrutide. The addition of GCGR agonism is hypothesized to lead to increased energy expenditure and decreased calorie intake, though the precise role of GCGR stimulation in retatrutide's WL mechanism remains unclear (48).

In people with history of T2D before RYGB, we found no significant differences in the gut hormone profiles that were measured following a MMTT. Our results suggest that these hormone profiles do not seem to be influenced by T2D remission nor relapse following MBS. Thus, other mechanisms are likely to predominate at regulating glycemic status once excessive body weight is no longer in the equation.

Previous studies identified that preoperative insulin therapy, HbA1c levels and T2D duration are key factors in predicting T2D remission (49–51). In the current study, although none of the participants were on insulin therapy before surgery, the T2D relapse group exhibited higher preoperative HbA1c levels and longer T2D duration, suggesting a more pronounced  $\beta$ -cell dysfunction and reduced pancreatic reserve, which may have contributed to the T2D relapse.

Although not significant, our T2D relapse group did not lose as much % of body weight as our T2D remission group at nadir. While most studies suggest that the initial WL following RYGB is related with long-term T2D-related outcomes (16, 52, 53), a recent study found that WL had an impact on T2D remission in the first year, but did not influence the relapse rate in subsequent years (54). Taken together, these findings highlight stressing the importance of implementing dietary and lifestyle modifications following the surgical intervention in order to optimize the WL and consequent metabolic benefits, as early weight reduction may improve  $\beta$ -cell function and insulin sensitivity—both critical for achieving and sustaining T2D remission.

Although this study provides valuable insights, some limitations should be acknowledged. First, its cross-sectional design does not allow a confirmation of a causal relationships between hormone profiles and clinical surgical outcomes. The strict inclusion criteria for cohort 2 (patients with T2D relapse who were not receiving

GLP-1 receptor agonists or insulin therapy; matched groups for pre-operative age, pre-operative BMI, time since surgery, and post-operative WL trajectories) were applied to avoid introducing bias into our results. Consequently, only 10 patients from our 10-year cohort qualified for the T2D relapse group. While this relatively small sample size, may limit the interpretation of the results, the detailed characterization of participants and the significant differences observed in their glucose and insulin profiles allowed us to investigate the impact of incretin hormones on these distinct metabolic profiles. Therefore, despite this limitation, the study provides valuable insights and supports the robustness of the findings. Additionally, although the type of RYGB procedure was not randomly assigned, the balanced distribution of surgical techniques reduces the potential for confounding. The influence of diabetes medications on meal test results, especially in cohort 2, should also be considered. To minimize this effect, only participants treated with metformin were included. Plasma glucose levels were measured using a glucometer, which has lower precision compared to laboratory-based plasma glucose measurements. However, since no part of the study protocol relied on real-time highly accurate glucose values, the method used for glucose measurement, although less precise, did not appear to raise significant concerns regarding the study's overall findings.

In conclusion, we aimed to understand whether the enteropancreatic hormone profile of patients subjected to RYGB could be responsible for the long-term suboptimal response to the surgery, both regarding WR or T2D relapse. Although our results point towards a potential role of both GLP-1 and GIP in WR, this warrants further research. In contrast, the enteropancreatic hormone profile does not seem to be influenced by T2D remission nor relapse following BMS, and other mechanisms seem to be at play, including the natural history of disease progression. Overall, our results highlight a possible link between altered incretin responses and WR after RYGB, and support further prospective trials targeting GLP-1/GIP pathways to improve long-term metabolic outcomes.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Centro Hospitalar de Entre Douro e Vouga (approval numbers: CA-0172/19-0t\_MP/AC and CA-149/ 2020-0t\_MP/AC). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

SA: Methodology, Investigation, Visualization, Formal Analysis, Writing – original draft. CL: Formal Analysis, Writing – review & editing, Investigation. MM: Writing – review & editing, Investigation. BH: Investigation, Writing – review & editing. JH: Investigation, Writing – review & editing. RA: Writing – review & editing, Investigation. MN: Investigation, Writing – review & editing. MM: Conceptualization, Investigation, Funding acquisition, Writing – review & editing. MG: Conceptualization, Project administration, Funding acquisition, Investigation, Writing – review & editing. SP: Writing – review & editing, Conceptualization, Investigation, Formal Analysis, Visualization, Funding acquisition, Project administration.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2025.1624001/full#supplementary-material>

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