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ORIGINAL CONTRIBUTIONS

Pre-operative Predictors of Weight Loss and Weight Regain Following Roux-en-Y Gastric Bypass Surgery: a Prospective Human Study

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Abstract

Background There are currently few pre-operative predictors of initial and long-term weight loss following bariatric surgery.
Objectives We evaluated the role of pre-operative patient characteristics and baseline gut and adipose-derived hormones in predicting maximal total body weight loss (WL_{max}) and risk of weight regain (WR) after Roux-en-Y gastric bypass (RYGB) surgery.
Methods One hundred five adult patients undergoing primary RYGB were prospectively recruited. Baseline demographics were recorded and fasting plasma glucose, glycosylated hemoglobin (A1C), insulin, glucagon, leptin, active ghrelin, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) levels were measured on day of surgery.
Results Our cohort had a mean age of 44.4 ± 13.0 years, and initial BMI (body mass index) of 45.1 ± 6.7 kg/m^2 with mean post-operative follow-up of 40 months. Eighty patients were female and 26 had type 2 diabetes mellitus (T2D). Average WL_{max} was 35.3 ± 7.4%. On univariate analysis, higher baseline fasting ghrelin, lower age, lower CRP (C-reactive protein), lower A1C, and negative T2D status were associated with greater WL_{max} ($p < 0.05$). Controlling for these variables using stepwise multivariate regression, only higher fasting ghrelin and younger age were associated significantly with greater WL_{max} ($p < 0.05$). In subgroup multivariate regression analysis of T2D patients, higher ghrelin and glucagon were significantly associated with greater WL_{max}. Following stepwise multivariate regression, lower initial BMI and lower glucagon were associated with greater WR ($p < 0.05$).
Conclusions Incorporation of baseline biological and hormonal markers may help in developing more accurate predictive models for weight loss following bariatric surgery that help inform patient counseling and decision-making.

Keywords Bariatric surgery · Type-2 diabetes · Ghrelin · Glucagon · GI hormones

Introduction

Obesity is a global epidemic and a risk factor for diabetes, cardiovascular diseases, cancer, and overall mortality. Bariatric surgery is the most effective therapy for obesity [1]. Laparoscopic Roux-en-Y gastric bypass (RYGB) is a highly effective treatment for morbid obesity, leading to weight loss, remission of obesity-associated comorbidities including type 2 diabetes (T2D), and reduction in long-term mortality [2].

Long-term follow-up studies of bariatric surgery patients suggest that most patients achieve durable weight loss, with a small subgroup that experiences inadequate weight loss after primary operation (non-responders) and a larger group that experience substantial weight regain after achieving adequate initial weight loss (weight regainers) [1, 3]. Factors predisposing patients to significant weight regain are unknown, but important to recognize as concern about weight regain is a significantly deterrent for surgery in patients considering bariatric surgery. This weight recidivism has important health consequences including recurrence of obesity-related comorbidities, as well as economic repercussions with recurrent costs associated with managing ongoing obesity and the associated conditions [4]. The ability to identify patients at risk of inadequate weight loss or weight regain remains therefore an important clinical priority.

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The potential predictive factors for long-term outcomes include patient demographics and comorbidities, behavioral and socioeconomic parameters, and biological factors. In a large prospective cohort study looking at pre-operative patient characteristics and post-operative behavior, only a few baseline variables such as age, race, and diabetes status were associated with post-operative weight change, and the effect size of these predictive variables was small [5]. Biological factors have been understudied, with only a few reports involving small cohorts and poor follow-up [6].

Collectively, there is good scientific data indicating that hormonal changes are responsible for weigh outcomes and metabolic effects of RYGB, but their clinical predictive ability has not been studied well. We were interested in studying correlation of pre-operative serum biomarkers, specifically hormones involved in weight and glucose regulation, to weight loss (WL) and weight regain (WR).

Considering cost and risks of bariatric surgery, it is important to identify the individuals who will benefit the most from intervention. Moreover, improved pre-operative predictors of surgical outcomes will allow for improved counseling of patients regarding weight regain or inadequate weight loss. This prospective human cohort study evaluates the role of pre-operative clinical, biochemical, and metabolic hormones in predicting weight loss and weight regain following laparoscopic RYGB.

Methods

Patients

The study protocol was reviewed and approved by our Institutional Review Board. Consecutive patients undergoing a primary laparoscopic RYGB by the senior author were offered to participate in the study as part of which fasting pre-operative blood values were collected. Inclusion criteria for this study included patients who successfully underwent a RYGB. One hundred and eight adult patients were initially included in the study. Three patients were excluded from the analysis, including 1 for the incidental intra-operative finding of a gastric GIST (gastrointestinal stromal tumor), 1 for intra-operative finding of cirrhosis, and 1 patient who had type 1 diabetes. The patients had a standard pre-operative evaluation including meetings with dieticians, psychologist, and the surgeon before being cleared for surgery. They underwent a standard laparoscopic RYGB surgery, with 10-cm Roux and 40-cm BP (biliopancreatic) limbs. The surgical technique remained unchanged for all patients. All patients were asked to go on a modified 2-week pre-operative diet to help with weight loss.

Demographic data including age, gender, and race were collected through questionnaire and patients' electronic records. Clinical outcomes were then followed by chart review and clinic visits. Patients with glycosylated hemoglobin (A1C) of 6.5% or above, or those with history of diabetes and taking diabetic medications before surgery, were considered T2D. Parameters of interest were pre-operative weight loss, maximal post-operative weight loss, and weight regain. These were defined as below.

Pre-operative Weight Change

Pre-operative weight loss was calculated as the highest weight recorded in 1 year before surgery minus the patient's weight at the last pre-operative visit, which was available for 103 (98.1%) patients.

Maximal Post-operative Weight Loss

Baseline weight and BMI (body mass index) were regarded as those recorded during the patients' final pre-operative visit, generally within 2 weeks prior to surgery. Post-operative weights were measured during in-person follow-up visits by qualified staff and were recorded for the following time points: 1 month, 6 months, and then annually up to 5 years. For the patients not following up with bariatric clinic, data was collected from the patients' electronic records.

In this study, weight changes were presented as percentage total body weight loss. Maximum %TBWL (WL_{max}) was calculated based on the recorded nadir weight within the first 2 years after surgery and their pre-operative weight.

For most of the patients, the nadir weight was reached between 1 and 2 years after surgery, so for the patients who missed both 1- and 2-year follow-ups ($N = 12$), WL_{max} was not calculated. These cases were removed from weight loss analysis. The baseline demographics of these patients, including BMI, age, and race, were similar to the overall cohort.

Weight Regain

For WR analysis, we included just the patients with at least a 3-year follow-up ($n = 49$). Weight regain was defined as percentage of WL_{max} that was regained at 3 years post-operatively. In other words, weight regain was calculated using the formula:

Maximal WR = (highest recorded weight after reaching nadir weight until 3 post-op years − nadir weight) × 100/(pre-op weight − nadir weight).

Biochemical and Hormonal Measurements

Blood samples were obtained pre-operatively by venipuncture after an overnight fast in the operating room, immediately after induction of anesthesia and before starting the surgical procedure. Blood samples were immediately sent to the hospital reference lab, Center for Clinical Investigation (CCI). Serum biochemical data including CRP (C-reactive protein), fasting glucose, A1C, insulin, leptin, glucagon, active ghrelin, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic

polypeptide (GIP) levels were measured by routine clinical chemistry, immediately after extraction by the LabCorp and BRAC (Brigham Research Assay Core) labs. Active (acylated) ghrelin was measured by radioimmunoassay (RIA). Preservative enzymes and pretreatment including acidifying solution for ghrelin and DPP4 inhibitor for GLP-1 and GIP were added to the EDTA (ethylenediaminetetraacetic acid) collection tubes. Serum samples for these hormonal measurements were immediately frozen and stored at − 80 °C until assayed together later.

Statistical Analysis

Variables are presented as mean ± standard deviation (SD). The quantitative data in counterpart groups were compared by *t* test. The chi-squared test was used to compare qualitative values. Single correlations among variables were evaluated with the Pearson coefficient of correlation. Multivariate linear regression models were constructed separately for weight loss and weight regain to ascertain the statistical significance of independent baseline predictors. For this multivariate analysis, pre-operative variables with $p < 0.2$ in univariate regression analysis were included. Analyses were performed with IBM SPSS Statistics for Windows, version 22.0., Armonk, NY: IBM Corp. and GraphPad Prism Software, version 7.03, La Jolla, CA. All reported *P* values are 2-sided. *P* values less than 0.05 are considered significant.

Results

Pre-operative Anthropometrics and Metabolic Parameters

The study cohort of 105 patients had a mean age, weight, and BMI of 44.4 ± 13.0 years, 125.0 ± 24.7 kg, and 45.1 ± 6.7 kg/m^2, respectively. Age ranged from 22 to 70 years and BMI from 35.0 to 77.3 kg/m^2. Twenty-five (23.8%) were male and 80 (76.2%) were female. Age (45.8 ± 12.3 vs. 44.0 ± 13.3 years, p = NS) and BMI (46.6 ± 8.3 vs. 44.7 ± 6.3, p = NS) were similar between men and women. Mean follow-up was 39.9 ± 26.8 months.

Twenty-six (24.8%) patients had T2D with 2 diet-controlled, 13 on oral medications, and 11 on insulin. The T2D patients were significantly older than non-diabetic (non-DM) patients (53.3 ± 9.6 vs. 41.5 ± 12.7 years, $p < 0.01$). However, there was no significant difference in M to F ratio. Table 1 summarizes demographic and baseline blood values of the overall cohort and compares the T2D and non-DM subgroups.

Post-operative Weight Loss

The mean %TBWL after surgery was 33.9 ± 7.4% after 1 year, 32.0 ± 9.2% after 2 years, 29.1 ± 8.2% after 3 years, 27.0 ± 8.8% after 4 years, and 25.7 ± 9.9% after 5 years (Fig. 1). Figure 1 also depicts follow-up rates in different time points. As expected, there was variation in weight loss outcomes (Supp. Figure 1). WL_{max} in male and female patients was 33.9 ± 7.3% and 35.7 ± 7.5% (p = NS). WL_{max} in T2D patients was significantly lower than non-DM patients (31.4 ± 6.2 vs 36.5 ± 7.4%; $p < 0.01$), as well as average %TBWL 6 months, 1, 2, and 3 years after surgery; however, this difference became non-significant after 4 years, likely due to decreased number of the patients (Fig. 1).

In a univariate linear regression analysis of the whole cohort, correlation between WL_{max} and pre-operative demographics, degree of pre-operative weight loss, and baseline hormone levels was calculated. Lower A1C, lower CRP, negative T2D status, higher active ghrelin, and younger age at surgery were significantly correlated with higher WL_{max} (Supp. Table 1). WL_{max} in patients younger than 60 years of age was significantly higher compared with older patients (36.3 ± 7.2% vs. 30.7 ± 6.9%; $p < 0.01$). Degree of perioperative WL was not significantly correlated with WL_{max} (p = 0.07). In a multivariable linear regression, only initial age and fasting active ghrelin remained significantly associated with WL_{max} ($p < 0.05$, Table 2).

T2D is an important comorbidity in many patients undergoing RYGB, and since weight loss can impact post-operative T2D outcomes, we performed a similar analysis to identify predictors of WL_{max} in the T2D patient subgroup. Univariate regression analysis shows correlation between higher pre-operative ghrelin and glucagon levels with greater WL_{max} (Supp. Table 1). In a multivariable linear regression model, higher fasting active ghrelin and fasting glucagon were correlated with greater WL_{max} in T2D patient cohort ($p < 0.01$, Table 2 and Fig. 2).

Weight Regain

For the overall cohort, average WR was 20.7 ± 13.5% of the maximum weight loss achieved. There was variability in the degree of weight regain, with approximately a third of the patients maintaining their weight (Supp. Figure 2). WR was not different between male and female genders (23.8 ± 14.5 vs. 19.8 ± 13.3%; p = NS). WR was also similar between different race groups, with 21.0 ± 12.9%, 22.4 ± 22.1%, and 18.3 ± 8.3% in white, African-American, and Hispanic races, respectively. It was also similar in the T2D vs. non-DM groups (23.4 ± 11.5% vs. 19.8 ± 14.1%; p = NS).

On univariate linear regression analysis, initial BMI, glucagon, leptin, and glucose were correlated with higher WR with p value of less than 0.2 (Supp. Table 2). Correlation of WL_{max} with later WR was not significant ($p = 0.10$). In multivariate linear regression analysis, lower baseline fasting glucagon level and lower initial BMI were correlated with greater weight regain ($p < 0.05$, Table 3).

Table 1 Post-operative WL_{max} and pre-operative characteristics of the patients in overall cohort and separately in non-DM and T2D subgroups

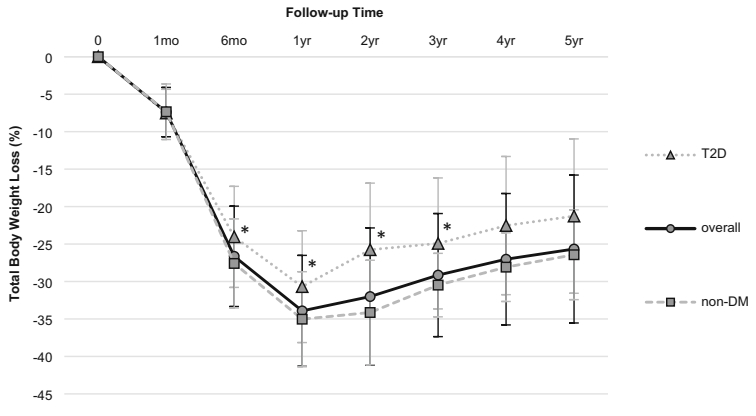
	Overall mean ± SD ($n = 105$)	Non-DM mean ± SD ($n = 79$)	T2D mean ± SD ($n = 26$)	p value (t test/chi-sq.)
WL_{max}	35.3 ± 7.4	36.5 ± 7.4	31.4 ± 6.2	< 0.01**
Gender (M:F)	25:80	16:63	9:17	0.14
Age (year)	44.4 ± 13.0	41.5 ± 12.7	53.3 ± 9.6	< 0.01**
Race (W:B:H)	71:16:15	53:13:12	18:3:3	0.80
Weight (kg)	125.0 ± 24.7	126.1 ± 24.7	121.7 ± 24.9	0.43
Initial BMI (kg/m^2)	45.1 ± 6.7	45.4 ± 6.2	44.2 ± 8.6	0.45
Pre-op WL (%)	4.6 ± 3.6	4.4 ± 3.6	5.0 ± 3.5	0.43
CRP (mg/l)	6.6 ± 6.1	6.1 ± 4.5	7.8 ± 8.9	0.24
Glucose (mg/dl)	101.5 ± 25.8	94.1 ± 15.4	124.6 ± 36.8	< 0.01**
A1C (%)	6.0 ± 0.9	5.7 ± 0.4	7.1 ± 1.2	< 0.01**
Insulin (IU/ml)	12.9 ± 18.8	9.0 ± 8.3	26.5 ± 33.6	< 0.01**
HOMA-IR	3.4 ± 5.3	2.2 ± 2.3	7.8 ± 9.2	< 0.01**
Glucagon (pg/ml)	64.3 ± 26.2	62.2 ± 27.7	69.6 ± 21.7	0.24
Leptin (ng/ml)	49.8 ± 30.1	52.6 ± 31.1	40.7 ± 25.2	0.10
Ghrelin (pg/ml)	54.9 ± 22.9	55.2 ± 22.1	54.1 ± 25.3	0.84
GLP-1 (pg/ml)	3.9 ± 2.8	4.1 ± 3.1	3.2 ± 1.7	0.45
GIP (pg/ml)	38.5 ± 23.7	36.2 ± 22.2	44.7 ± 28.4	0.43

SD, standard deviation; *non-DM*, non-diabetic; *T2D*, type 2 diabetes; *chi-sq.*, chi-square test; WL_{max}, maximal total body weight loss; *M*, male; *F*, female; *W*, white; *B*, black; *H*, Hispanic; *BMI*, body mass index; *WL*, weight loss; *CRP*, C-reactive protein; *A1C*, glycosylated hemoglobin; *HOMA-IR*. homeostasis model assessment of insulin resistance; *GLP-1*, glucagon-like peptide 1; *GIP*, glucose-dependent insulinotropic polypeptide; *$p < 0.05$; **$p < 0.01$

Discussion

Weight Loss

Weight loss following RYGB is an important outcome measure for both patients and surgeons. Significant post-operative WL is associated with resolution or remission of obesity-related comorbidities, improved quality of life, and reduced long-term mortality [7]. Variability in outcomes after bariatric surgery is well documented [1], and optimizing WL after surgery remains a challenge in management of bariatric patients. The reasons behind this variability remains poorly understood. Several attempts at correlating patient phenotypes with post-operative outcomes have failed to identify significant factors. Although patient dietary choices are often cited as an explanation for this variability, the main reason is likely



Time after surgery	0	1mo	6 mo	1yr	2yr	3yr	4yr	5yr
Overall n	105	105/105	97/105	90/101	67/92	50/83	42/72	27/53
Follow up rate (%)	100	100	92.4	89.1	72.8	60.2	58.3	50.6
%TBWL (mean ± SD)	0	-7.4 ± 3.3	-26.6 ± 6.7	-33.9 ± 7.4	-32.0 ± 9.2	-29.1 ± 8.2	-27.0 ± 8.8	-25.7 ± 9.9

Fig. 1 Average TBWL (total body weight loss; %) following Roux-en-Y gastric bypass (RYGB) in overall cohort, and separately in non-DM and T2D patients. Non-DM, non-diabetic; T2D, type 2 diabetes; SD, standard deviation; *$p < 0.05$

Table 2 Multivariate linear regression analysis models for association of WL_{max} with pre-operative demographic and metabolic factors, in overall cohort (R-squared = 0.22, $F = 10.68$, $p < 0.01$) and T2D patients (R-squared = 0.60, $F = 13.52$, $p < 0.01$)

		Standardized coefficient beta	p value
Overall cohort	Age (year)	− 0.36	0.001**
	Ghrelin (pg/ml)	0.31	0.004**
T2D patients	Ghrelin (pg/ml)	0.57	0.001**
	Glucagon (pg/ml)	0.45	0.008**

WL_{max}, maximal total body weight loss; *T2D*, type 2 diabetes; **$p < 0.01$

multifactorial with at least some biological determinants [8]. Genetic association studies support that biology can drive success as WL outcomes correlate with genetic factors such as serotonin receptor [9] or UCP-2 genes [10], and several single-nucleotide polymorphisms (SNPs) [11–14]. Routine genetic assessment of potential bariatric patients is however challenging and expensive, and association of these factors with WL outcomes is weak and the effect size is small.

In this study, we set out to identify pre-operative serum biomarkers to help us assess outcomes following RYGB. We prospectively enrolled 105 patients undergoing RYGB and measured pre-operative hormone levels to see if we can identify pre-surgical markers that can help predict post-operative outcomes. Our patients experienced the majority of weight loss in the first 12 months after surgery with 75% of them reaching their nadir weight at 1-year time point.

Ghrelin, a peptide-secreted predominantly by the gastric enteroendocrine cells, stimulates food intake and growth hormone (GH) secretion. Ghrelin is found in the circulation in both acylated (active) and des-acylated forms. Only the acylated form (active ghrelin as measured in our study) acts at the GHS-R1a to affect appetite, GH release, and metabolism [15]. Our study showed a significant positive correlation between WL_{max} and baseline fasting active ghrelin levels. A previous rodent RYGB study had similarly demonstrated that pre-operative ghrelin levels are correlated to WL [16]. The importance of pre-operative ghrelin level on 1 year weight loss data was also demonstrated in a small study of 15 patients undergoing laparoscopic sleeve gastrectomy [17]. Our data is also consistent with Labayen et al. findings in a dietary weight loss study showing that lower baseline ghrelin levels were correlated with resistance to fat mass loss [18]. In contrast to our study, Pellitero et al. [19] found that pre-operative total ghrelin was lower in patients with higher WL 12 months after RYGB, and total ghrelin was not a predictor of patients who maintained their WL at 12 to 24 months after surgery. This difference in finding however may be explained by our measurement of active (acylated) ghrelin, which is not necessarily reflected in total ghrelin levels. Furthermore, the patients in this study underwent a modified version of the RYGB (ringed or a distal bypass), which likely affects hormonal changes and outcomes.

Our finding is biologically plausible, as high active ghrelin levels are associated with increased appetite, and therefore, those with higher levels of this hormone may benefit most from appetite suppressing/anorexic effects of bariatric surgery.

Fasting glucagon level also had a significant positive correlation with WL_{max} in T2D subgroup of patients. Glucagon is an amino acid peptide that is secreted from pancreatic α-cells in response to low levels of blood glucose. Non-glycemic effects of glucagon include modulation of food intake and satiety, lipid homeostasis, insulin secretion, and energy expenditure [20]. In non-surgical models, chronic administration of glucagon has been shown to substantially reduced body weight (up to 25%) in diet-induced obese (DIO) mice [21, 22]. Although glucagon studies in RYGB are limited, our results support the aforementioned studies indicating the role of glucagon in weight modification and suggest it might be used as a predictor of weight outcome after bariatric surgeries among T2D patients.

Looking at other serum biomarkers, there was no correlation between WL_{max} and pre-operative gut derived incretin hormones GLP-1 and GIP. Similarly, Werling et al. showed that GLP-1 (and PYY; peptide YY) did not correlate to WL after RYGB [23].

Based on multivariate analysis, we find that patient age also has a significant inverse correlation with WL_{max}. Most published studies concur with our findings, showing better WL in younger patients [24, 25]. Similarly, sex, baseline weight, and initial BMI were not found to correlate with WL_{max}, consistent with reports by Courcoulas et al. on 3-year weight outcomes of the Longitudinal Assessment of Bariatric Surgery (LABS) cohort

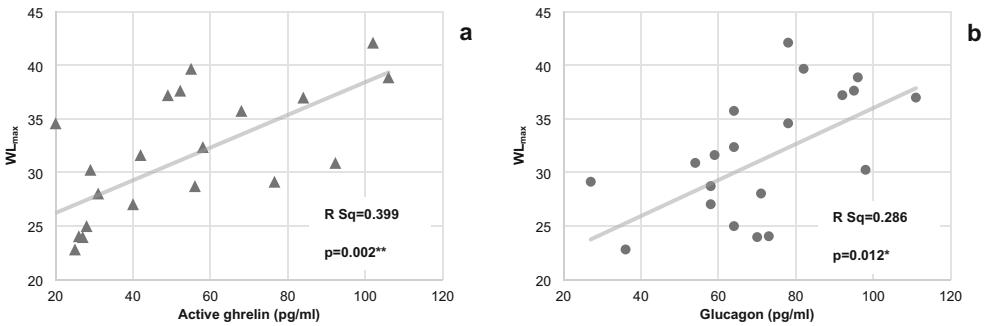


Fig. 2 Linear correlation of post-operative WL_{max} with pre-operative **a** active ghrelin and **b** glucagon in type 2 diabetic subgroup of patients. WL_{max} = maximal total body weight loss; R Sq = R-squared; *$p < 0.05$; **$p < 0.01$

Table 3 Multivariate linear regression analysis models for association of WR with pre-operative demographic and metabolic factors, in overall cohort (R-squared = 0.21, $F = 5.24$, $p = 0.010$) and non-DM patients (R-squared = 0.28, $F = 5.26$, $p = 0.012$)

		Standardized coefficient beta	p value
Overall cohort	Initial BMI (kg/m^2)	− 0.35	0.018*
	Glucagon (pg/ml)	− 0.31	0.037*
Non-DM patients	Initial BMI (kg/m^2)	− 0.37	0.032*
	Glucagon (pg/ml)	− 0.35	0.044*

WR, weight regain; *non-DM*, non-diabetic; *BMI*, body mass index; *$p < 0.05$

[5]. We found that T2D is significantly correlated with less WL after RYGB in univariate analysis, but this was not confirmed in multivariate regression. There are several studies using univariate-like analysis suggesting that T2D leads to less favorable weight outcomes [5, 26, 27]. However, when we perform a multivariate analysis and control for differences in fasting ghrelin and the higher age of the diabetic cohort, the T2D effect washed out. Specifically, these analyses highlight the importance of ghrelin levels in influencing post-operative weight loss, a parameter not examined in prior studies. Because weight loss in T2D patients undergoing RYGB is particularly important and can impact T2D outcomes, we performed a separate analysis to identify predictors of WL in this subgroup and found that similar to the overall cohort, ghrelin is correlated with WL_{max}. Specific to the T2D subgroup, however, higher glucagon levels are also correlated to WL_{max}. Considering smaller number of patients in our T2D subgroup, more studies are needed to evaluate and validate this finding.

Our findings are novel in that we have identified hormonal factors that influence post-RYGB outcomes, suggesting that there are biological factors that influence post-operative outcomes. As we were primarily interested in identifying pre-operative markers of post-operative outcomes, we did not measure post-surgery levels of the same hormones, which can be the subject of future studies. Since we focused on pre-operative factors, we also did not include post-operative eating habits and activity levels which have been proposed as factors influencing outcomes, although previous studies have confirmed that their contribution may be limited [28]. We believe larger prospective studies are needed to validate this finding with the ultimate goal of assessing pre-operative hormone profile of patients to educate them on their likely maximal weight loss and help to improve patient education and consent.

Weight Regain

Although some degree of weight regain is commonly seen after patients reach their nadir weight, several patients experience *significant* weight regain and concern about this possibility lowers many patients' enthusiasm for bariatric surgery. Identifying pre-operative factors which may predict risk of post-operative weight gain are therefore very important in helping providers council patients. There are various definitions for significant weight regain after bariatric surgeries. One of the most commonly used definitions is gaining > 20% of the maximal initial weight loss [29, 30]. In a national study of bariatric surgery patients with 7 years of follow-up, Courcoulas et al. defined 6 trajectories for weight outcome patterns after RYGB [31], with the trajectories being distinguishable at 3 years. Based on this data, we chose the 3-year time point to study weight regain in our cohort.

Our data identified lower baseline fasting glucagon level and lower initial BMI were correlated with greater WR. Some studies have highlighted the importance of initial weight loss on subsequent weight regain, including a study by Cooper et al. who showed that greater initial WL leads to more successful long-term weight outcomes (less WR) [32]. In our study, WL_{max} however was not a significant predictor of WR when controlling for biological hormonal factors. T2D status also did not influence risk of WR. This suggests that different mechanisms may be at play and influence these outcomes.

The role of leptin on post-operative weight loss and subsequent WR is unclear with mixed results in rodent studies [33, 34]. Although there was a trend towards this in our univariate analysis, we could not confirm this on our multivariate analysis. Age, sex, and race did not show a correlation with WR in our study, consistent with the mixed literature on this topic [35].

This study is unique and practical in that it tries to link fasting pre-operative hormone levels to long-term outcomes in a prospective fashion; this is an approach that can be replicable in a clinical setting. It does however have some limitations including high rate of female patients which is inherent to most bariatric studies, and low follow-up rates beyond 3 years. Although we believe a 3-year follow-up is long enough to establish weight regain patterns and has been used in other studies [1, 36], longer follow-ups are needed for confirmatory future studies. This study focused on RYGB, which at the time of initiation of the study remained a very popular surgical option. With current changes in bariatric surgical options and popularity of sleeve gastrectomy, we plan to perform similar studies looking at outcomes of sleeve gastrectomy patients too.

Conclusions

In this study, we have assessed the ability of pre-operative clinical and serum metabolic biomarkers to predict maximum WL and WR after LRYGB. We found that higher pre-operative ghrelin and younger age are associated with greater

maximum weight loss (WL_{max}), and lower baseline BMI and glucagon levels were associated with greater WR. These findings could help guide larger future studies to confirm and ultimately be used to develop a care protocol that involves measurements of these hormones in the pre-operative phase and the data used to discuss individual level likelihood of weight regain and more accurate prediction of weight loss after RYGB. Such discussions will improve shared decision-making with the patient and pre-operative counseling.

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Compliance with Ethical Standards

Conflict of Interest Ali Tavakkoli is cofounder and consultant for AltrixBio with an equity stake in the company. Eric Sheu is consultant for Medtronic. All the other authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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