

# Roux-en-Y gastric bypass increases glycaemic variability and time in hypoglycaemia in patients with obesity and pre-diabetes/type 2 diabetes mellitus: a prospective cohort study

**Short Running Title:** Glycaemic variability increases after RYGB

## Authors

<sup>1</sup>Ibiyemi Ilesanmi\*, <sup>1</sup>George Tharakan\*, <sup>1</sup>Kleopatra Alexiadou\*, <sup>1</sup>Preeshila Behary, <sup>1</sup>Haya Alessimii, <sup>1</sup>Candace Bovill-Taylor, <sup>1</sup>Julia Kenkre, <sup>1</sup>Sirazum Choudhury, <sup>1</sup>Chedie Doyle, <sup>2</sup>Sanjay Purkayastha, <sup>2</sup>Alex Miras, <sup>2</sup>Christos Tsironis, <sup>1</sup>Harvinder Chahal, <sup>1</sup>Stephen R. Bloom, <sup>1</sup>Nick S. Oliver, <sup>2</sup>Ahmed R. Ahmed, <sup>3</sup>Bernard Khoo, <sup>1</sup>Tricia M-M. Tan<sup>†</sup>

\*equal contribution

<sup>1</sup>Department of Metabolism, Digestion and Reproduction, Imperial College London, London W12 0HS, UK.

<sup>2</sup>Department of Surgery and Cancer, Imperial College Healthcare NHS Trust, London W2 1NY, UK.

<sup>3</sup>Endocrinology, Division of Medicine, Royal Free Campus, University College London, London NW3 2PF, UK.

<sup>†</sup>Corresponding author

Prof Tricia M-M. Tan

Division of Diabetes, Endocrinology and Metabolism

Section of Investigative Medicine

6th Floor Commonwealth Building

Imperial College London

Du Cane Road, London W12 0HS

Email: [t.tan@imperial.ac.uk](mailto:t.tan@imperial.ac.uk); Tel: 020 75942665

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## KEYWORDS

Roux-en-Y Gastric Bypass; Glycaemic variability; Post Bariatric Hypoglycaemia

## **Abstract**

**Objective:** Roux-en-Y gastric bypass (RYGB) is an established treatment for type 2 diabetes.

The study objective was to establish RYGB's effects on glycaemic variability (GV) and hypoglycaemia.

**Research Design and Methods:** Prospective observational study of 10 participants with pre-diabetes/Type 2 diabetes undergoing RYGB, studied before surgery (Pre), 1 month (1m), 1 year (1y) and 2 years (2y) post-surgery with continuous glucose measurement (CGM). A mixed meal test (MMT) was performed at Pre, 1m and 1y. [ClinicalTrials.gov NCT01945840]

**Results:** After RYGB, mean CGM glucose fell (at 1m, 1y and 2y), and GV increased (at 1y and 2y). Fifty percent (5/10) of participants exhibited a percentage time in range  $<3.0$  mmol/L [54 mg/dl] (%TIR $<3.0$ ) greater than the consensus target of 1% at 1y or 2y. Peak glucagon-like peptide-1 (GLP-1) and glucagon area-under-curve (AUC) during MMT were respectively positively and negatively associated with contemporaneous %TIR $<3.0$ .

**Conclusions:** Patients undergoing RYGB are at risk of developing post-bariatric hypoglycaemia due to a combination of reduced mean glucose, increased GV and increased GLP-1 response.

At present, bariatric and metabolic surgeries such as Roux-en-Y gastric bypass (RYGB) are the most effective means of achieving durable weight loss and remission of diabetes in obesity and type 2 diabetes mellitus (1). There is evidence that intra-day glycaemic variation (GV) may be exaggerated after surgery (2; 3). Aetiologically linked is the phenomenon of post-bariatric hypoglycaemia (PBH), where patients present with disabling hypoglycaemic episodes, sometimes necessitating hospital admission (4). Post-operative CGM studies have suggested that hypoglycaemic events can occur in 29-75% of patients (5-7). Our objective was to comprehensively profile the longitudinal evolution of GV and hypoglycaemia after RYGB and to study their relationship to the post-prandial glycaemic and enteropancreatic hormone response.

## **Research Design and Methods**

This was a prospective observational study conducted according to the principles of the Declaration of Helsinki (ClinicalTrials.gov NCT01945840; UK National Health Service Health Research Authority West London National Research Ethics Committee 13/LO/1510) (8). Participants underwent study visits prior to RYGB (Pre), one month (1m), one year (1y) and 2 years (2y) after surgery. Volunteers then had a 3 hour MMT (4) at the Pre, 1m and 1y timepoints utilising Ensure Compact® (13 g protein, 11.6 g fat, 36 g carbohydrates, 330 kcal, 137.5 ml – Abbott Nutrition). Blood was sampled at baseline, 15, 30, 60, 120, and 180 minutes from time of meal ingestion, via an indwelling cannula placed in the ante-cubital fossa. The participants were fitted with a blinded G4 Platinum or G6 CGM system (Dexcom) at each study visit; these CGM systems have been validated for accuracy (9) and comparability (10) in the hypoglycaemic range. Data were collected for up to 7 days, under free living conditions, and were analysed using the EasyGV v10 calculator for measures of GV and percentage time in

range (%TIR) (11; 12). For details on statistical and assay methods, see the Supplementary File.

## Results

The clinical characteristics of the 10 patients recruited are shown in Supplementary Table 1. Following surgery, participants demonstrated substantial improvements in weight, HbA1c, fasting glucose and insulin, and hepatic insulin sensitivity (Supplementary Figure 1 and Supplementary Table 1), with stabilisation between 1y and 2y in line with accepted experience after RYGB (1). No participant during this study reported any symptoms, nor were admitted for treatment of hypoglycaemia.

GV increases after RYGB at 1y and 2y; the combination of reduced mean glucose and increased GV are associated with increased time in hypoglycaemia

Supplementary Figure 2 shows a progressive reduction of mean CGM glucose, stabilising between 1y and 2y. GV, as measured by percentage coefficient of variation (%CV), continuous overlapping net glycaemic action (CONGA), and mean absolute glucose (MAG) was not significantly different at 1m, but demonstrated significant increases at 1y and 2y; mean amplitude of glucose excursions (MAGE) was significantly increased at 2y but not 1y. In line with the substantial reduction of mean CGM glucose at 1m, 1y and 2y, the %TIR>10.0 mmol/L [180 mg/dl] fell (Supplementary Table 1). Notably, at 1m, the combination of reduced mean glucose with unchanged GV was associated with no significant change in %TIR<3.0 mmol/L [54 mg/dl] and <3.9 mmol/L [70 mg/dl]. After 1m, the combination of reduced mean glucose and increased GV was associated with significant rises in %TIR<3.0 and <3.9 (Supplementary Table 1 and Figure 1). Supplementary Figure 3 shows that six participants had a %TIR<3.9

above the ATTD international consensus desired target of 4% and five had a %TIR<3.0 above the target of 1% (13), either at 1y or 2y. %TIR<3.0 was negatively correlated with mean CGM glucose (Spearman correlation coefficient -0.55), and positively correlated with %CV (0.61), MAG (0.53) and CONGA (0.42) but not MAGE. In multivariable linear mixed model analysis utilising these parameters as covariates, only %CV ( $p=0.034$ ) remained significantly associated with %TIR<3.0.

Peak GLP-1 and glucagon AUC during MMT are associated with time in hypoglycaemia

Figure 1 and Supplementary Table 2 show that there were post-surgical enhancements in post-prandial GLP-1 and a reduction of glucagon secretion during the MMT paralleling the improvement in glucose tolerance (14). We hypothesised that the following parameters derived from the MMT study at each timepoint might be associated with the contemporaneous %TIR<3.0 and <3.9: fasting levels of glucose, GLP-1, insulin and glucagon; Cmax values of glucose, GLP-1, insulin and glucagon; overall and incremental AUC<sub>0-180</sub> for each of these hormones; and the nadir value of glucose achieved during the MMT. %TIR<3.9 was positively correlated with peak value of GLP-1 (0.68), GLP-1 AUC<sub>0-180</sub> (0.63) and negatively with fasting glucose (correlation coefficient -0.59), and glucagon AUC<sub>0-180</sub> (-0.50). Given the *a priori* co-linearity of GLP-1 peak and GLP-1 AUC<sub>0-180</sub>, these parameters were tested individually in the multivariable models. Only the peak value of GLP-1 and Glucagon AUC<sub>0-180</sub> remained significantly associated with %TIR<3.9 ( $p=0.0129$  and  $0.003$  respectively). When tested for associations with %TIR<3.0, both these parameters were also significantly associated (GLP-1 peak,  $p=0.024$ ; Glucagon AUC<sub>0-180</sub>,  $p=0.01$ ).

## Discussion

In this study we show that RYGB is followed by increases in GV at the 1y and 2y timepoints; the combination of the fall in mean glucose with increased GV is associated with significant rises in time in hypoglycaemia. Limitations of the study include the relatively short duration CGM at 7 days which limits the interpretation of the GV and %TIR compared to those established by longer-term CGM studies (15), the small number of subjects studied and the fact that most participants had well controlled glycaemia on lifestyle measures alone. Strengths include the metabolic homogeneity of the cohort, use of a standardised surgical technique in a single centre, and the prospective design with serial MMT studies that allowed us to relate the emergence of CGM-detected hypoglycaemia to contemporaneous post-prandial glycaemic and enteropancreatic hormone responses. Our data support the hypothesis that PBH is associated with excessive GLP-1 secretion and additionally a possible association with reduced glucagon secretion during the MMT. Consistent with this, both the GLP-1 receptor antagonist exendin(9-39) (16) and glucagon itself (17) are being investigated as potential therapies for PBH.

We highlight two fundamental challenges in the diagnosis of PBH. Firstly, there is a symptomatic 'gap' between CGM-detected hypoglycaemia and PBH; although many of our participants had CGM-detected hypoglycaemia, none reported symptoms diagnostic of PBH. Secondly, there is currently no gold-standard test for PBH. Our data suggest that the nadir glucose during an MMT is not predictive of CGM-detected hypoglycaemia. Defining PBH either via symptoms or hospital admission for hypoglycaemia, via provocation tests such as MMT, or via CGM-detected hypoglycaemia presents a diagnostic challenge.

We conclude that a substantial proportion of patients undergoing RYGB for treatment of diabetes and obesity are at risk of developing hypoglycaemia and this should be disclosed as a common adverse effect during pre-surgical counselling. On the other hand, it should be noted that an equal proportion of patients did not develop long-term CGM-detected hypoglycaemia, and it is unclear why this phenomenon occurs in some patients and not others. Further research will be required in the form of long-term longitudinal studies of patients undergoing RYGB, focusing on risk factors for increased GV and the development of symptomatic and asymptomatic hypoglycaemia, and relating these phenomena to their clinical outcomes. The data from such studies will have important implications for the diagnosis and management of PBH.

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## Author Contributions

G.T., I.I., P.B., K.A., C.B-T., J.K., S.C., H.A., C.D., A.M., H.C., A.A., C.T., S.P., S.R.B., T.M-M.T. contributed to the execution of the clinical study. S.R.B., T.M-M.T. designed the study. C.T., A.A., S.P. performed the surgery in the prospective RYGB cohort. N.S.O. contributed to discussion and interpretation of CGM data. B.K. prepared the statistical analysis. B.K., G.T., I.I., K.A., T.M-M.T. wrote and edited the manuscript. All authors reviewed the final manuscript. T.M-M.T. is the guarantor of this work, had full access to the data, and accepts full responsibility for integrity of the data and the accuracy of the data analysis.

## Funding

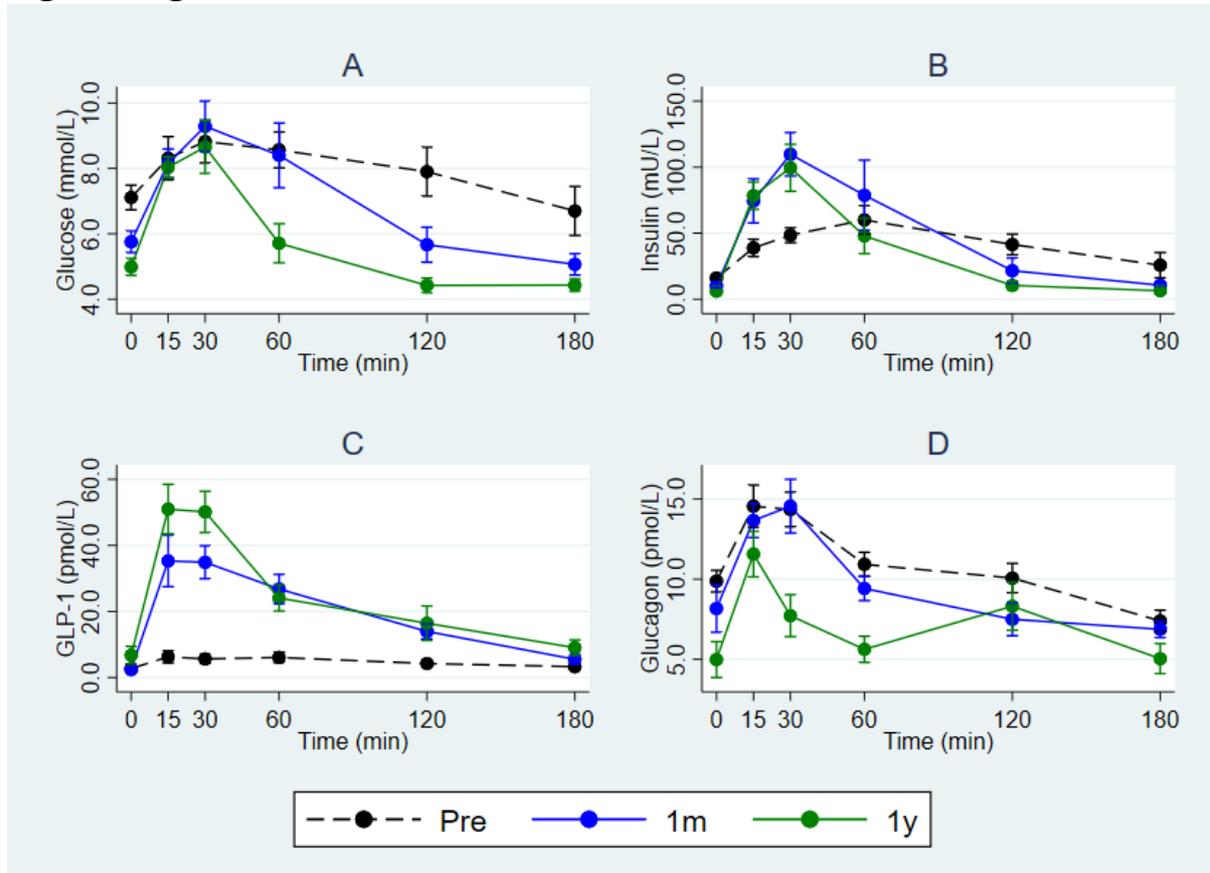
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necessarily those of the abovementioned funders, the UK National Health Service (NHS), the NIHR, or the UK Department of Health.

#### Conflict of Interest Statement

N.O. has received grants, personal fees and non-financial support from Dexcom, and grants from Roche Diabetes outside the submitted work. All other authors report no potential conflicts of interest.

## Figure Legend



**Figure 1:** Response of Glucose (A), Insulin (B), Glucagon-Like Peptide-1 (GLP-1 – C), Glucagon (D) to MMT given at time 0, plotted as mean and SEM over time (Pre: pre-surgery, dashed black line; 1m: 1 month post-surgery, solid blue line; 1y: 1 year post-surgery, solid green line).

# Supplementary Material for ‘Roux-en-Y gastric bypass increases glycaemic variability and time in hypoglycaemia in patients with obesity and pre-diabetes/type 2 diabetes mellitus: a prospective cohort study’

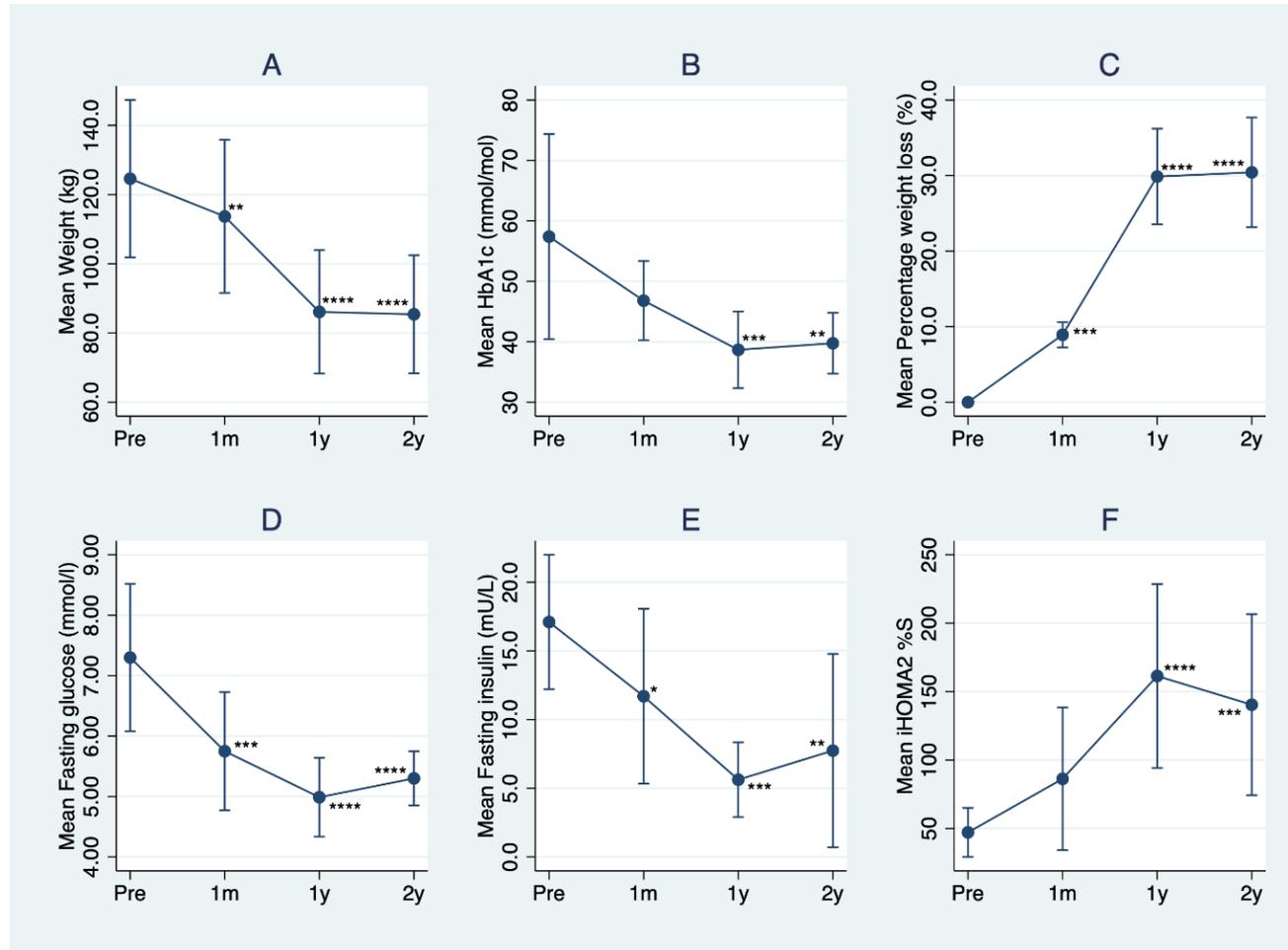
## **Power Calculation and Statistical Analysis**

Data and statistical analysis used Prism 8.2.1 (GraphPad Software) and STATA 15.1 (STATACorp LLC). A power calculation for a repeated measures one-way ANOVA suggested that a sample size of 8 participants had 90% power at an alpha of 0.05 to detect clinically significant changes in mean CGM of 2.5 mmol/L [45 mg/dl], equivalent to a change in HbA1c of 17 mmol/mol, and percent coefficient of variation (%CV) of 10%, a difference which has been linked to significantly increased risks of hypoglycaemia during treatment of patients with type 2 diabetes (18). The trapezoid method was used to calculate area under curve over the 180 minute MMT study (AUC<sub>0-180</sub>). A one-way repeated measures ANOVA with Bonferroni correction (reported as adjusted p-values) was used to compare GV metrics. For analysis of the MMT data, a linear mixed model repeated measures analysis was used, with Bonferroni correction. To examine the relationship of %TIR<3.0 mmol/L [54 mg/dl] and %TIR<3.9 mmol/L [70 mg/dl] with CGM and MMT parameters, the univariable association of these parameters was initially tested using Spearman correlation. A multivariable linear mixed model, incorporating those parameters found to have statistically significant associations, was then used to examine the relationship of significantly correlated parameters with %TIR. For comparison of the %TIR values through time, a non-parametric Friedman test was used.

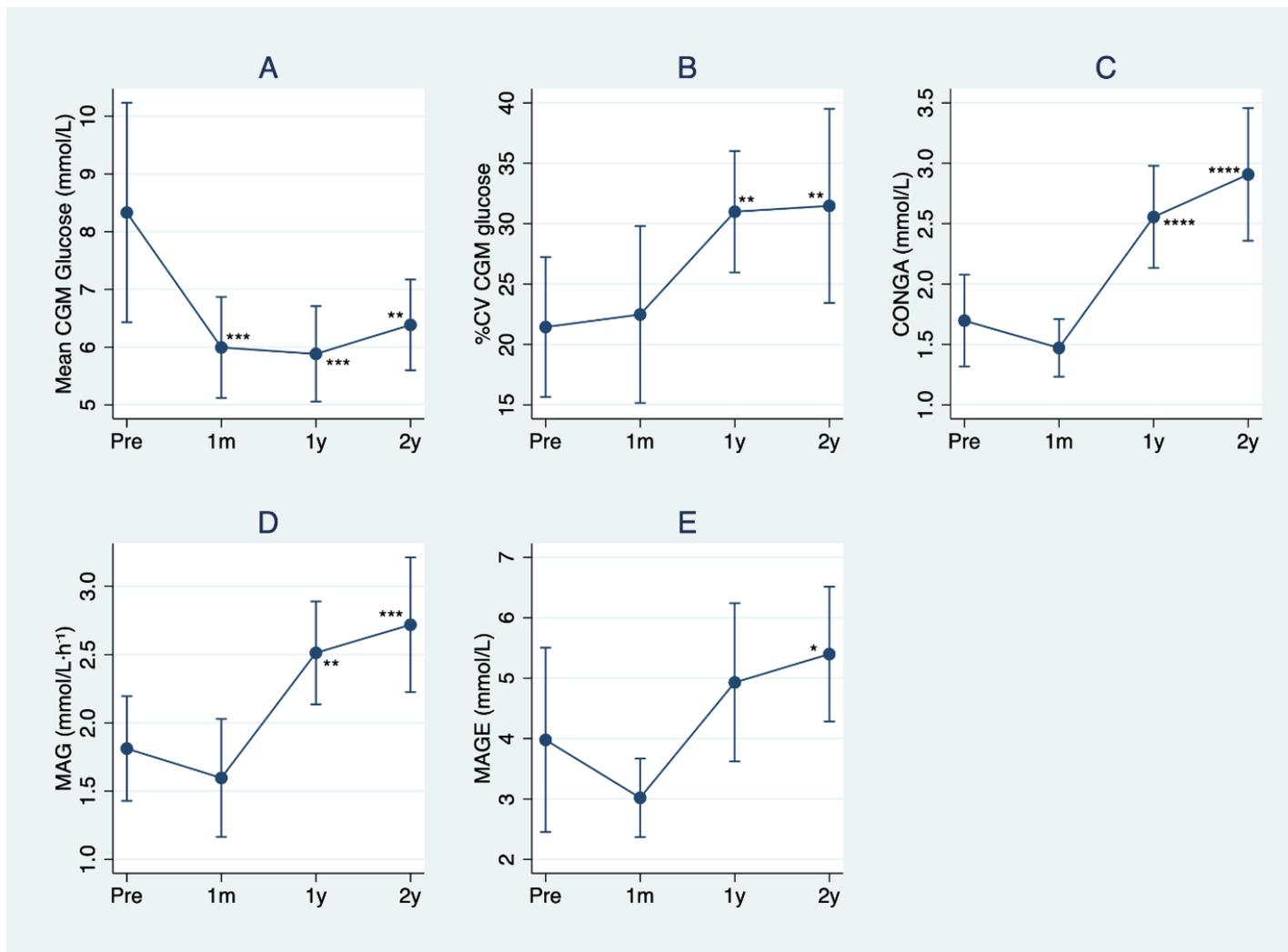
## **Assay Techniques**

Blood for glucose was collected in fluoride oxalate tubes, for insulin in plain (serum) tubes, for gut hormones in Lithium heparin tubes containing Aprotinin (Nordic Pharma) and the DPP-IV inhibitor Diprotin A (Enzo Life Sciences). Glucose and insulin levels were measured by NW London Pathology (Abbott Architect; CVs <5%, <10% respectively). Active glucagon-like peptide-1 (GLP-1) levels were measured by a customised Milliplex magnetic bead-based multi-analyte, metabolic panel immunoassay (Millipore). The intra-assay and inter-assay coefficient of variation for active GLP-1 was <10%. The lowest limit of detection was 0.8 pmol/L. Glucagon was measured using an ELISA (Merckodia AB) with the high-stringency 'Alternative' protocol to eliminate cross-reaction with other proglucagon-derived peptides (14): there was a detection limit of 1.5 pmol/L and intra-assay and inter-assay coefficient of variation of <10%.

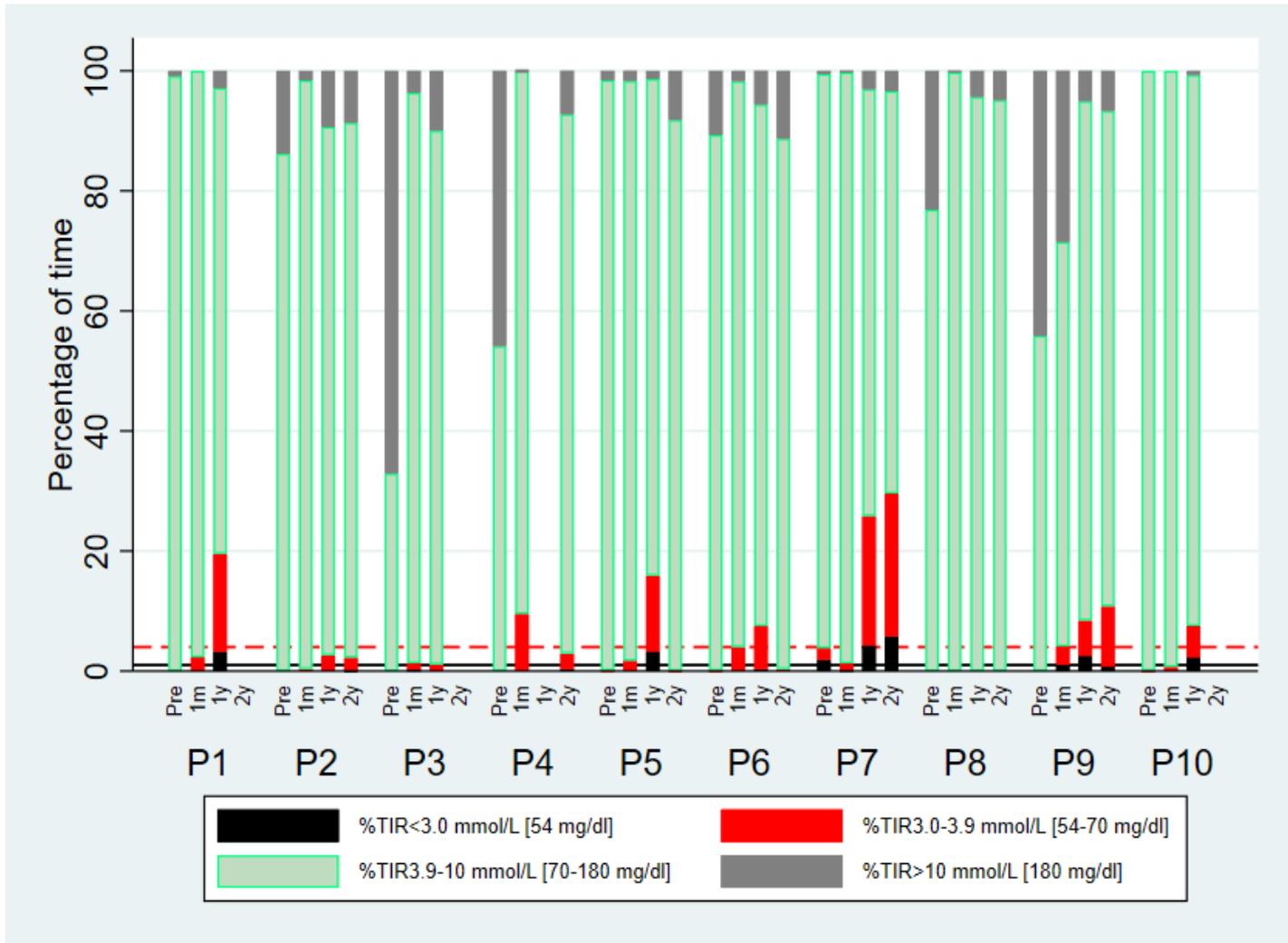
## Supplementary Figures



**Supplementary Figure 1:** Plots of weight (A), HbA1c (B), percentage weight loss (C), fasting glucose (D), fasting insulin (E), 24-variable interactive homeostatic model assessment with default settings (iHOMA2 – (19) percentage insulin sensitivity (F) in prospective RYGB cohort over time (Pre: pre-surgery, 1m: 1 month post-surgery, 1y: 1 year post-surgery, 2y: 2 years post-surgery). Mean and SD plotted. \* p<0.05, \*\* p<0.01, \*\*\* p<0.001, \*\*\*\* p<0.0001 for comparison with Pre (one-way repeated measures ANOVA with Bonferroni correction).



**Supplementary Figure 2:** Measures of mean glycaemia and glycaemic variability (11) in the RYGB cohort. Mean CGM glucose (A), percentage coefficient of variation (%CV – B), Continuous Overall Net Glycaemic Action (CONGA – C), Mean Absolute Glucose (MAG – D), Mean Amplitude of Glycaemic Excursions (MAGE – E) plotted as mean and SD over time (Pre: pre-surgery, 1m: 1 month post-surgery, 1y: 1 year post-surgery, 2y: 2 years post-surgery). One-way repeated measures ANOVA with Bonferroni correction for A-E. Adjusted p-value symbols: \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ , \*\*\*\*  $p < 0.0001$  for comparison with Pre.



**Supplementary Figure 3:** Post-surgical evolution of percentage time in range (%TIR) (Y-axis) in the RYGB cohort <3.0 mmol/L [54 mg/dl] (black), 3.0-3.9 mmol/L [54-70 mg/dl] (red), 3.9-10.0 mmol/L [70-180 mg/dl] (light green outline), >10.0 mmol/L [180 mg/dl] (grey). These data are plotted as stacked bar graphs, grouped per participant (indicated by P1, P2 etc.) and the time-point for each bar graph is labelled next to the X-axis. Horizontal dashed red line indicates International Consensus for %TIR<3.9 target at <4% and horizontal black line indicates International Consensus for %TIR<3.0 target cut-off in patients with T2DM at <1%.

## Supplementary Tables

**Supplementary Table 1:** Clinical and metabolic characteristics of the prospective Roux-en-Y Gastric Bypass (RYGB) cohort at the study time points. All participants were diagnosed with diabetes or pre-diabetes, and had RYGB surgery performed at the IWC between 2016 and 2018. All participants were followed up pre-surgery (Pre) and at 1m. Nine of the cohort were assessed at 1y. The remaining patient did not attend this assessment but returned for assessment at the 2y mark. A total of 9 participants were assessed at the 2y timepoint. One participant's data at the 2y timepoint was not analysed as she was pregnant at the time. Another participant's CGM data at 2y was not available due to failure of the CGM to collect enough data for adequate analysis, but the clinical and metabolic data have been included in the analysis. Data displayed as mean  $\pm$  SD or median (range) for Percentage Time in Range. N/A, not applicable. iHOMA2, 24-variable interactive homeostatic model assessment using default settings, %B indicates estimated beta-cell function and %S indicates estimated insulin sensitivity (19). %TIR, Percentage Time in Range to 3 significant figures. One-way repeated measures ANOVA with Bonferroni correction used for parametric measures. Adjusted p-value symbols: \* p<0.05, \*\* p<0.01, \*\*\* p<0.001, \*\*\*\* p<0.0001 for comparison with Pre. Friedman test used for comparison of %TIR values from Pre to 1y and 2y timepoints. † p<0.05, †† p<0.01

	Pre	1m	1y	2y
<b>Number analysed</b>	10	10	9	8
<b>Treatment (Diet/Metformin)</b>	9/1			
<b>Age at surgery (yr)</b>	50.2 $\pm$ 13.2	N/A	N/A	N/A
<b>Gender (M/F)</b>	2/8	2/8	2/7	2/6
<b>Weight (kg)</b>	124.6 $\pm$ 22.7	113.7 $\pm$ 22.2**	86.1 $\pm$ 17.8****	85.4 $\pm$ 17.1****
<b>Weight loss (%)</b>	0	8.9 $\pm$ 1.7***	29.9 $\pm$ 6.3****	30.4 $\pm$ 7.3****
<b>HbA1c (IFCC mmol/mol)</b>	57.4 $\pm$ 17.0	46.8 $\pm$ 6.6	38.7 $\pm$ 6.3***	39.8 $\pm$ 5.0**
<b>HbA1c (converted to NGSP %)</b>	7.4 $\pm$ 1.56	6.4 $\pm$ 0.60	5.7 $\pm$ 0.58***	5.8 $\pm$ 0.46**
<b>Fasting glucose (mmol/L)</b>	7.3 $\pm$ 1.2	5.8 $\pm$ 1.0***	5.0 $\pm$ 0.7****	5.3 $\pm$ 0.5****
<b>Fasting insulin (mU/L)</b>	17.1 $\pm$ 4.9	11.7 $\pm$ 6.4*	5.6 $\pm$ 2.7***	7.7 $\pm$ 7.0**
<b>iHOMA2 %B</b>	82.7 $\pm$ 17.9	96.8 $\pm$ 32.0	82.3 $\pm$ 44.2	83.3 $\pm$ 51.8
<b>iHOMA2 %S</b>	47.1 $\pm$ 17.9	86.3 $\pm$ 52.1	161.4 $\pm$ 67.2****	140 $\pm$ 66.2***
<b>%TIR&lt;3.0 mmol/L [54 mg/dl]</b>	0 (0-1.91)	0 (0-1.09)	2.27 (0-4.30)†	0.07 (0-5.81)†
<b>%TIR&lt;3.9 mmol/L [70 mg/dl]</b>	0 (0-3.83)	1.51 (0-9.52)	7.53 (0-25.8)†	2.24 (0-29.6)†
<b>%TIR3.9-10.0 mmol/L [70-180 mg/dl]</b>	87.7 (32.9-99.9)	97.2 (67.4-99.8)	86.9 (71.1-95.7)	89.1 (67.0-95.2)
<b>%TIR&gt;10.0 mmol/L [180 mg/dl]</b>	12.3 (0-67.1)	0.92 (0-28.5)	4.33 (0.67-9.95)	6.97 (3.40-11.3)

**Supplementary Table 2:** Summary of fasting, maximal concentration (Cmax), time of maximal concentration (Tmax), area under curve over 180 min (AUC<sub>0-180</sub>), incremental area under curve over 180 min (Inc AUC<sub>0-180</sub>) in glucose, insulin, GLP-1, glucagon during MMT before surgery (Pre), 1 month (1m) and 1 year (1y) after surgery. Nadir glucose is defined as lowest glucose after the peak. Mean ± SD are shown except for Tmax which are noted as median (IQR). Linear mixed model (repeated measures) with Bonferroni correction. \* indicates adjusted p-values for contrast between Pre and indicated timepoint after surgery where \* p<0.05, \*\* p<0.01, \*\*\* p<0.001, \*\*\*\* p<0.0001.

		Pre	1m	1y
<b>Glucose</b>	Fasting (mmol/L)	7.1±1.1	5.8±1.0***	5.0±0.8****
	Cmax (mmol/L)	9.3±2.0	9.7±2.2	9.3±1.9
	Nadir glucose (mmol/L)	6.7±2.2	5.0±1.0*	4.1±0.6***
	Tmax (min)	30 (15-30)	30 (15-30)	30 (15-30)
	AUC <sub>0-180</sub> (mmol·min/L)	1437±324	1245±306*	1008±153****
	Inc AUC <sub>0-180</sub> (mmol·min/L)	231±107	300±134	247±89
<b>Insulin</b>	Fasting (mU/L)	16.1±3.9	10.2±5.0****	6.1±3.2****
	Cmax (mU/L)	71.8±30.8	122.0±62.8***	115.1±46.4**
	Tmax (min)	60 (30-60)	30 (30-60)	30 (15-30)
	AUC <sub>0-180</sub> (mU·min/L)	7757±2876	8822±5341	6440±3006
	Inc AUC <sub>0-180</sub> (mmol·min/L)	4877±2537	7143±4953	5417±2600
<b>GLP-1</b>	Fasting (pmol/L)	2.7±3.3	2.5±2.9	6.8±7.5*
	Cmax (pmol/L)	8.3±4.3	43.7±19.3****	61.6±19.8****
	Tmax (min)	30 (15-60)	30 (15-30)	15 (15-30)
	AUC <sub>0-180</sub> (pmol·min/L)	904±539	3532±1223****	4282±1396****
	Inc AUC <sub>0-180</sub> (mmol·min/L)	430±231	3150±1230****	3400±1409****
<b>Glucagon</b>	Fasting (pmol/L)	9.9±2.0	9.1±4.8	5.0±2.7**
	Cmax (pmol/L)	15.8±2.8	21.1±17.0	12.8±3.4
	Tmax (min)	30 (15-30)	30 (15-30)	30 (15-30)
	AUC <sub>0-180</sub> (pmol·min/L)	1941±241	1932±855	1288±383*
	Inc AUC <sub>0-180</sub> (mmol·min/L)	416±166	709±472	522±313

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