

Supplemental Material

Title: Role of the gut in the temporal changes of β -cell function after gastric bypass in individuals with and without diabetes remission.

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Consort Diagram

Supplemental Figure 1: Consort Diagram

Supplemental Figure 2: Change in Disposition Index from pre-surgery to the latest time point after surgery

Supplemental Figure 3: Relationship of O-BCGS and post-prandial glucose at 120 minutes in the entire cohort and by remission status

Supplemental Figure 4: Relationship between ISR and plasma glucose during OGTT and GGI

Supplemental Figure 5: Glucose curves during GGI

Supplemental Table 1: Subject characteristics entire cohort

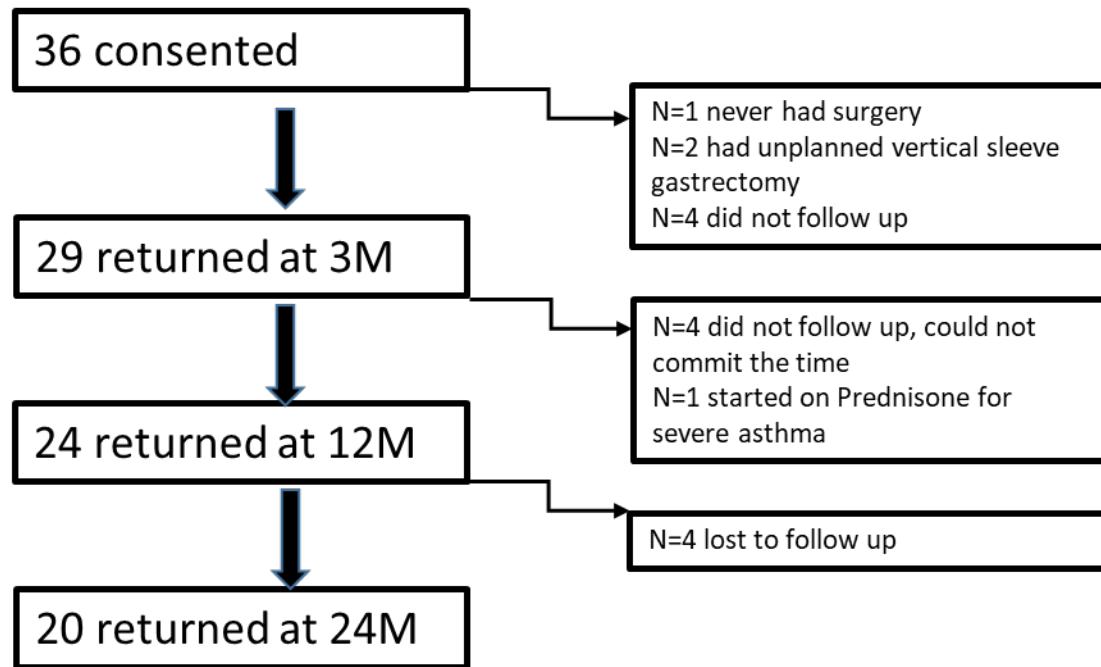
Supplemental Table 2: Change of β -cell function during oral and GGI challenges by remission status

Supplemental Table 3: Univariate predictive models

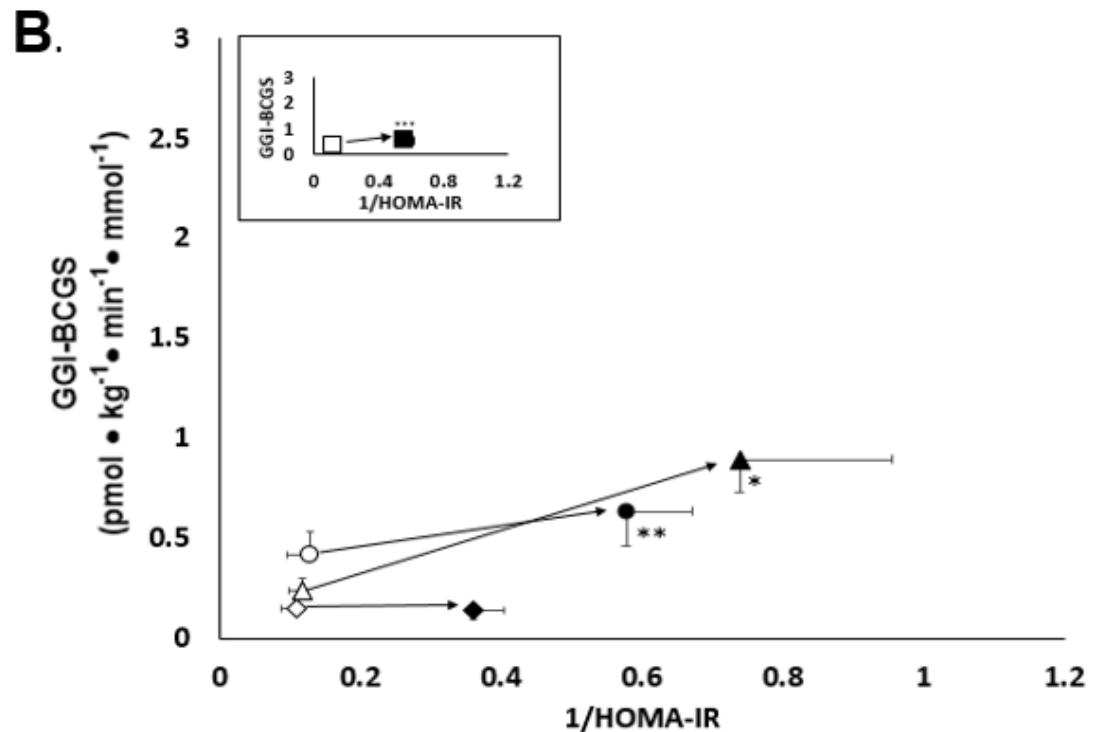
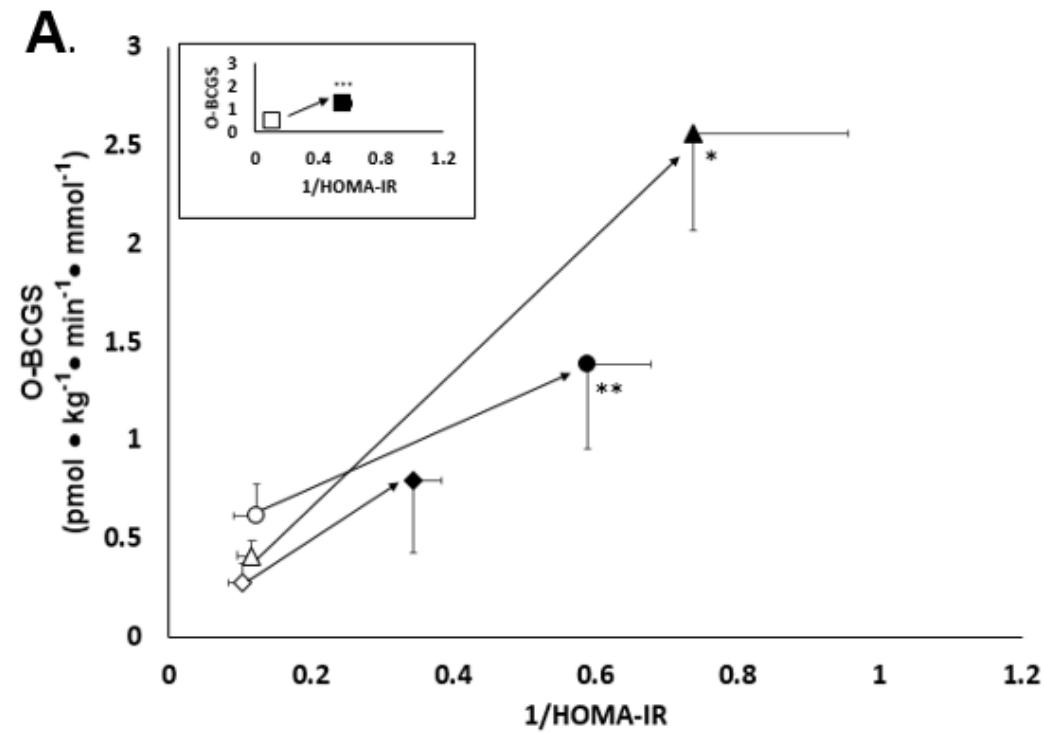
Supplemental Table 4: Univariate logistic regression

Supplemental Table 5A: Bivariate predictive model of longterm HbA1c

Supplemental Table 5B: Bivariate logistic regression: prediction of diabetes remission status

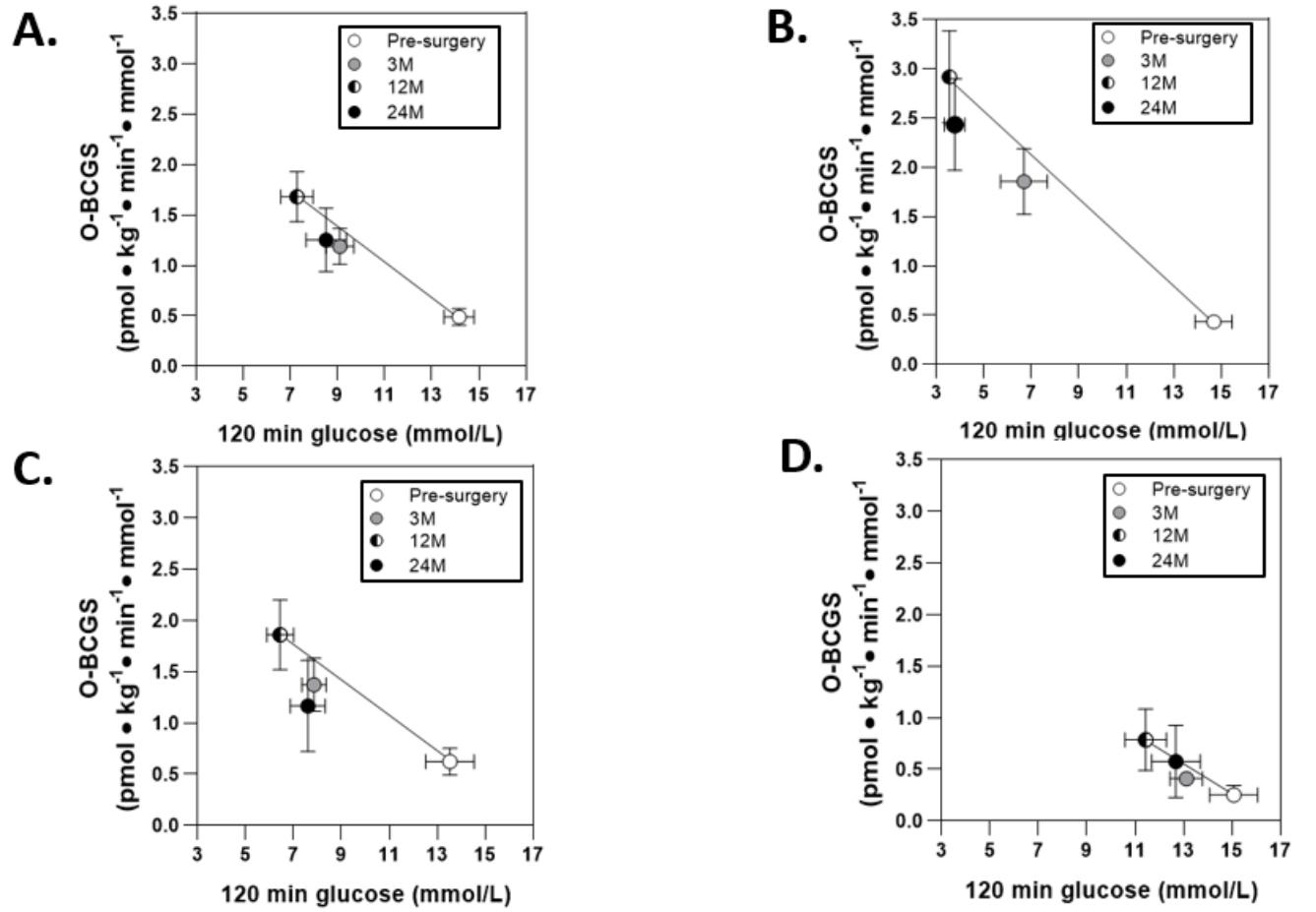


Supplemental Figure 1: Consort Diagram

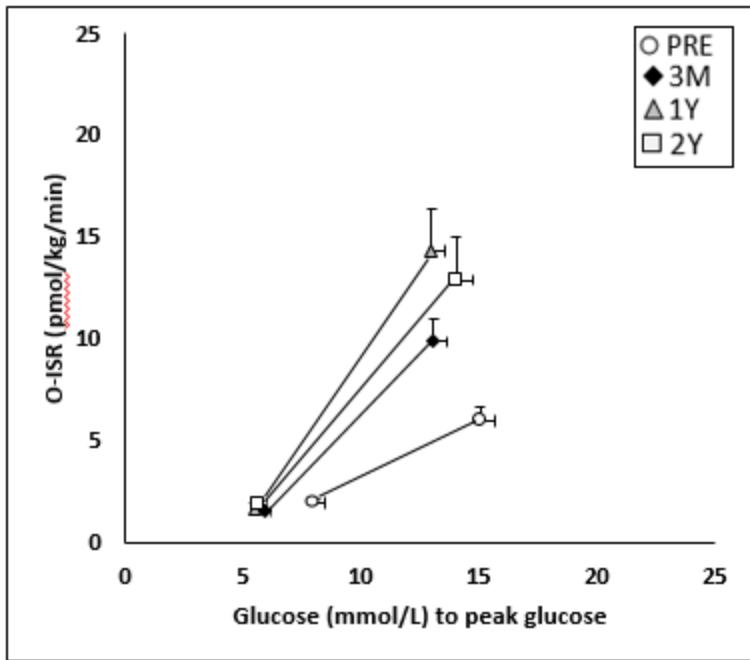
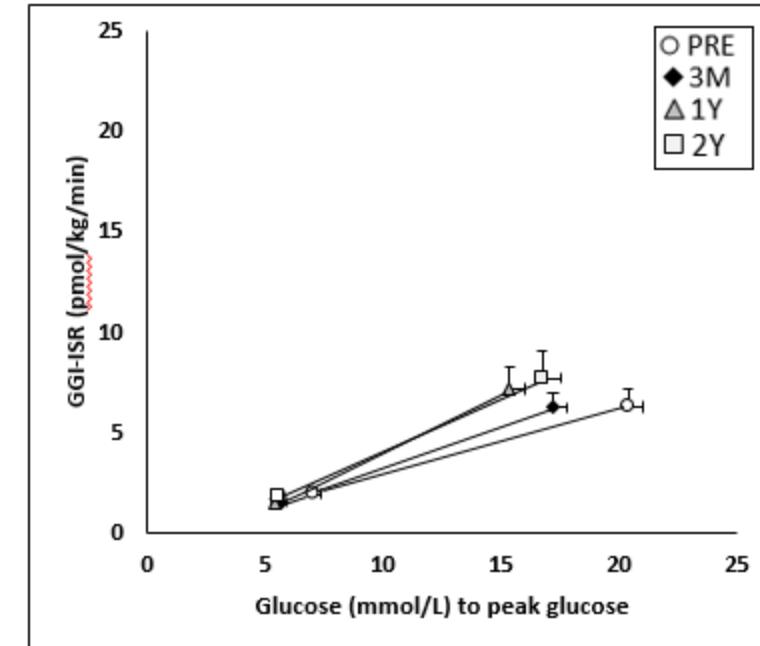


Supplemental Figure 2: Change in Disposition Index from pre-surgery to the latest time point after surgery

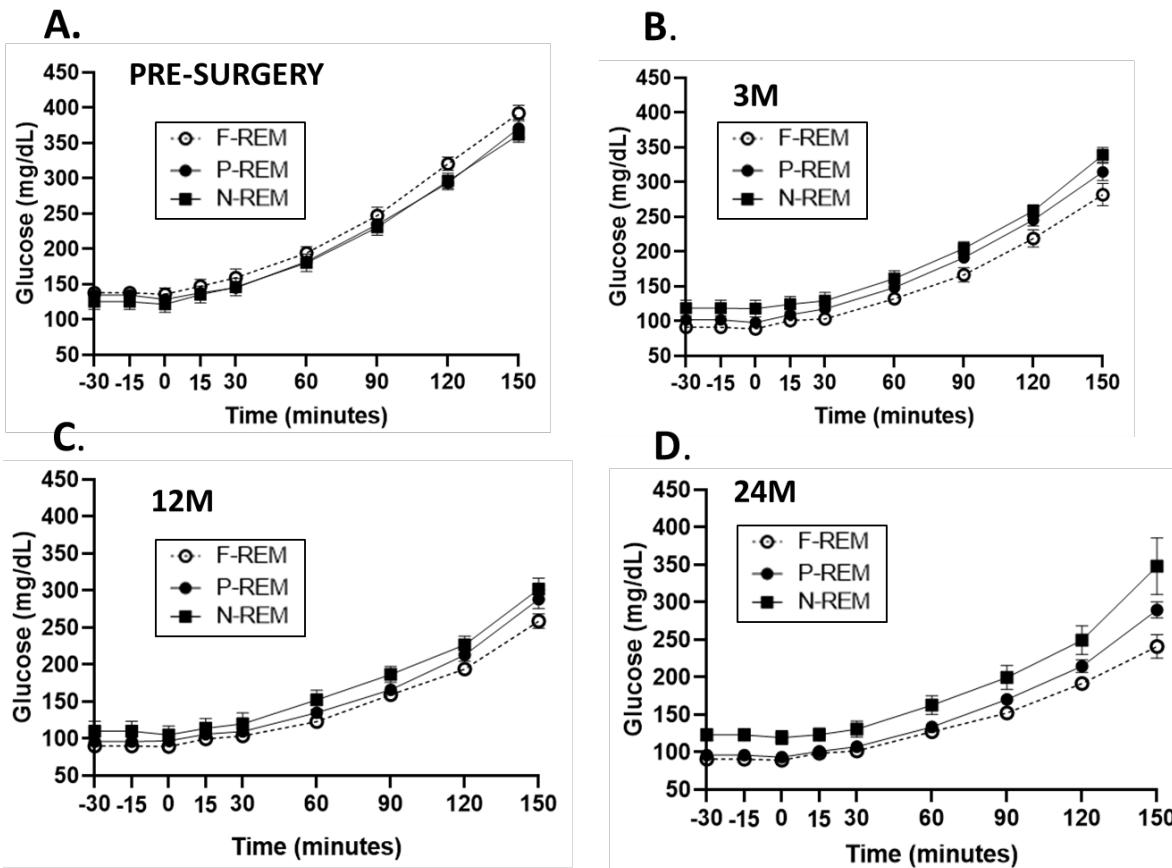
Relationship between beta cell function and $1/\text{HOMA-IR}$ in response to (A) OGTT and (B) GGI in F-REM (\blacktriangle), P-REM (\bullet), and N-REM (\blacklozenge). Open symbols, pre-surgery; closed symbols, latest time point 1 or 2 years after surgery. Inset: Whole Cohort; Mean \pm SEM. * Corresponds to comparison between pre-surgery disposition index vs. disposition index at latest time point. ***P<0.001; **P<0.01; *P<0.05



Supplemental Figure 3: Relationship of O-BCGS and post-prandial glucose at 120 minutes in the entire cohort (A), in F-REM (B), P-REM (C) and N-REM (D)

A.**B.**

Supplemental Figure 4: Relationship between ISR and plasma glucose during OGTT (A) and GGI (B)



Supplemental Figure 5: Glucose curves pre-surgery (A), at 3M (B), 12M (C), and 24 M (D) in F-REM (open circle), P-REM dark circle, and N-REM (back square)

	Pre-Surgery	3M	1Y	2Y
Gender (women/men)	23/6	23/6	20/4	19/1
Subjects on oral T2DM medication (n)	22/29	14/29	4/24	3/20
Subjects using insulin (n)	9/29	2/29	3/24	2/20
HbA1c % [¥]	7.82 ± 1.09	6.29 ± 0.97 ^{a***}	6.18 ± 0.96 ^{a***}	6.45 ± 1.31 ^{a***}
Weight (kg)	114.3 ± 19.3	94.9 ± 16.8 ^{a**}	84.0 ± 18.0 ^{a***}	81.3 ± 19.1 ^{a***}
BMI (kg/m ²)	42.38± 4.63	35.23 ± 4.4 ^{a***}	31.18 ± 5.2 ^{b***}	31.20 ± 6.3 ^{b***}
Weight loss (%)		17.0 ± 4.0 ^a	27.0% ± 7.0% ^b	27.0 ± 11.0 ^b
Fat mass (kg)	56.62 ± 12.10	45.34 ± 10.82 ^{a**}	39.65 ± 6.51 ^{a***}	40.05 ± 10.71 ^{a***}
Fat mass loss (%)		21.02 ± 13.82 ^a	30.39 ± 16.03 ^a	28.16 ± 13.00 ^a
Waist Circumference (cm)	122.5 ± 11.6	109.2 ± 15.7 ^{a**}	101.1 ± 14.0 ^{a***}	99.8 ± 16.6 ^{a***}
Hip circumference (cm) [¥]	127.8 ± 10.1	108.4 ± 16.0 ^{a**}	99.84 ± 14.40 ^{a***}	99.85 ± 16.56 ^{a***}
Waist/Hip Ratio [¥]	0.97 ± 0.08	0.94 ± 0.14 ^a	0.89 ± 0.06 ^a	0.90 ± 0.06 ^a
SBP (mm Hg) [¥]	126.2 ± 17.8	126.5 ± 18.6 ^a	121.6 ± 20.7 ^a	120.6 ± 19.2 ^a
DBP (mm Hg)	77.0 ± 13.4	76.7 ± 10.5 ^a	74.3 ± 11.5 ^a	75.0 ± 8.9 ^a
HOMA-IR [¥]	12.42 ± 6.46	3.79 ± 2.41 ^{a***}	2.73 ± 1.37 ^{a***}	2.64 ± 1.69 ^{a***}
fICR (mL/kg/min) [¥]	11.17 ± 6.56	22.02 ± 11.70 ^{a***}	30.51 ± 25.71 ^{a***}	38.34 ± 18.46 ^{b***}
O-ICR(mL/kg/min) [¥]	10.82 ± 5.28	13.83 ± 5.49 ^a	21.20 ± 18.61 ^{b**}	22.92 ± 15.21 ^{b**}

Supplemental table 1: Subjects characteristics

Mean ± SD. **p<0.01;***p<0.001 different from pre-surgery by one-way ANOVA post-hoc multiple comparison tests; Different letter superscripts indicate differences between post-surgery (3M, 12M, and 24M) conditions, by one-way ANOVA post-hoc multiple comparison tests at p<0.001 level; Variables denoted by (¥) are not normally distributed and analysis done with log-transformed data.

	Presurgery			3M			12M			24M		
	F-REM	P-REM	N-REM	F-REM	P-REM	N-REM	F-REM	P-REM	N-REM	F-REM	P-REM	N-REM
O-ISR AUC (pmol/kg*180 min) [‡]	937±438 ^a	867±417 ^a	446±326 ^b	1200±333 ^a	1111±619 ^a	636±268 ^a	1008±152 ^a	1319±708 ^a	976±913 ^a	1253±150 ^a	1220±843 ^a	1020±846 ^a
O-ISR iAUC (pmol/kg*180 min) [‡]	528±393 ^a	468±293 ^a	207±166 ^b	917±328 ^a	813±541 ^a	403±209 ^b	779±150 ^a	1030±640 ^a	575±441 ^a	958±87 ^a	8519±725 ^a	7017±787 ^a
O-BCGS (pmol kg ⁻¹ min ⁻¹ mmol ⁻¹) [‡]	0.43±0.14 ^a	0.62±0.53 ^a	0.25±0.26 ^b	1.86±0.74 ^{a*} ***	1.37±1.04 ^{a*} *	0.41±0.19 ^b	2.43±0.93 ^{a*} **	1.86±1.24 ^{a**} *	0.79±0.73 ^b	2.92±0.81 ^{a*} **	1.17±1.47 ^a	0.58±0.86 ^a
O-DI [‡]	0.05±0.01 ^a	0.06±0.07 ^a	0.03±0.03 ^a	1.02±0.59 ^{a*} **	0.47±0.48 ^{a**} *	0.11±0.10 ^b	1.49±1.11 ^{a**} *	0.83±0.55 ^{a***}	0.18±0.21 ^b	2.10±0.75 ^{a**} *	0.40±0.39 ^{a***}	0.23±0.38 ^b
O-early IGI [‡]	53.5±45.2 ^a	116±162 ^a	22.6±33.3 ^a	168±90 ^a	180±198 ^a	44.5±38.2 ^a	201±153 ^a	165±159 ^a	30.2±30.5 ^a	210±154 ^a	157±149 ^a	36.3±33.2 ^b
O-total IGI [‡]	41.8±37.2 ^a	63.4±84.1 ^a	19.2±8.45 ^a	73.3±44.7 ^a	84.7±100.3 ^a	17.8±10.7 ^b	75.4±39.7 ^a	68.8±61.4 ^a	15.3±3.98 ^b	61.0±41.5 ^a	67.7±71.8 ^a	13.6±10.6 ^b
GGI-ISR AUC (pmol/kg*180 min) [‡]	583±134 ^a	651±415 ^a	295±181 ^b	533±111	573±347	397±243	578±98 ^a	658±346 ^a	3328±343 ^b	779±121 ^a	634±199 ^a	365±195 ^b
GGI-ISR iAUC (pmol/kg*180 min) [‡]	250±123 ^a	323±350 ^a	124±85.3 ^b	326±72 ^a	336±295 ^a	185±177 ^a	349±59.9 ^a	415±293 ^a	116±92.4 ^b	502±152 ^{a*}	356±174 ^a	147±129 ^b
GGI-BCGS (pmol kg ⁻¹ min ⁻¹ mmol ⁻¹) [‡]	0.24±0.11 ^a	0.40±0.39 ^a	0.14±0.12 ^a	0.36±0.17 ^a	0.39±0.41 ^a	0.20±0.17 ^a	0.58±0.16 ^{a*}	0.68±0.70 ^a	0.14±0.10 ^b	0.95±0.38 ^{a**}	0.61±0.64 ^a	0.14±0.11 ^a
GGI-DI [‡]	0.07±0.08 ^a	0.04±0.05 ^a	0.02±0.01 ^a	0.20±0.14 ^{a*}	0.15±0.18 ^{a*}	0.06±0.07 ^b	0.33±0.18 ^{a**}	0.31±0.32 ^{a***}	0.05±0.06 ^b	0.66±0.19 ^{a**}	0.36±0.47 ^{a***}	0.07±0.04 ^a
fICR (ml/kg/min) [‡]	14.8±3.54 ^a	11.2±6.62 ^a	8.79±7.74 ^a	29.3±9.70 ^a *	21.8±11.1 ^a ***	18.0±13.2 ^a ***	25.3±5.16 ^a **	28.4±11.7 ^a **	38.5±49.6 ^a	46.7±35.2 ^a	39.2±15.5 ^a ***	32.8±14.8 ^a **
O-ICR (ml/kg/min) [‡]	13.2±5.53 ^a	10.8±5.40 ^a	9.43±5.02 ^a	14.8±5.90 ^a *	12.1±4.76 ^a	16.8±5.85 ^a *	14.5±8.39 ^a	17.8±9.91 ^{a**}	33.0±31.8 ^{a**}	28.1±23.6 ^a *	15.1±7.92 ^{ab}	33.4±15.1 ^{ac} **

Supplemental Table 2: Change of β -cell function and insulin clearance during oral and GGI challenges by remission status

Data are given as mean \pm SD. Different letter superscripts indicate statistically significant differences between groups at each condition by one-way ANOVA post-hoc multiple comparison tests at $p<0.05$ level. * $p<0.05$; ** $p<0.01$; *** $p<0.001$ indicate within group differences from pre-surgery; Variables denoted by (¥) are not normally distributed and statistical analysis was done with log-transformed data.

Baseline	0' glucose			120' glucose			HbA1c			HOMA-IR		
	B	R ²	p	B	R ²	p	B	R ²	p	B	R ²	p
Diabetes duration	0.357	0.128	0.087	0.554	0.307**	0.005	0.414	0.172*	0.039	0.264	0.069	0.213
Insulin use	0.441	0.195*	0.031	0.681	0.463***	<0.001	0.668	0.446***	<0.001	0.489	0.239*	0.015
HbA1c	0.446	0.199*	0.029	0.432	0.187*	0.035	0.483	0.234*	0.014	0.526	0.277**	0.008
HOMA-IR	0.511	0.261*	0.011	0.893	0.035	0.381	0.056	0.003	0.792	0.704	0.495***	<0.001
O-DI	-0.220	0.048	0.302	-0.493	0.243*	0.014	-0.316	0.100	0.124	0.271	0.073	0.201
O-BCGS	-0.262	0.069	0.216	-0.504	0.254*	0.012	-0.400	0.160*	0.048	-0.087	0.007	0.688
GGI-DI	-0.164	0.027	0.453	-0.495	0.245*	0.016	-0.298	0.089	0.157	-0.182	0.033	0.407
GGI-BCGS	-0.259	0.067	0.233	-0.449	0.202*	0.032	-0.318	0.101	0.130	-0.122	0.015	0.580
Early change, 0-3M												
Body weight	-0.182	0.033	0.395	-0.160	0.025	0.456	-0.029	0.001	0.892	-0.182	0.033	0.395
Fat mass	0.099	0.010	0.670	0.439	0.192*	0.047	0.301	0.091	0.173	0.099	0.010	0.670
Waist circumference	-0.001	0.000	0.998	-0.038	0.001	0.869	-0.001	0.000	0.996	-0.001	0.000	0.998
HbA1c	-0.101	0.010	0.645	0.241	0.058	0.268	0.215	0.046	0.313	-0.101	0.010	0.645
120' glucose	0.641	0.411**	0.001	0.634	0.402**	0.001	0.183	0.034	0.380	-0.118	0.014	0.584
HOMA-IR	0.340	0.116	0.104	0.398	0.159	0.054	0.473	0.223*	0.017	-0.117	0.014	0.586
O-BCGS	0.029	0.001	0.895	0.105	0.011	0.625	0.507	0.257*	0.010	0.527	0.278**	0.008
GGI-BCGS	-0.006	0.000	0.978	0.291	0.085	0.175	0.582	0.338**	0.003	0.220	0.048	0.314
eIGI	-0.137	0.019	0.523	0.145	0.021	0.499	0.534	0.285**	0.006	0.367	0.135	0.078
Total change (0-12/24M)												
Body weight	0.119	0.014	0.580	-0.038	0.001	0.862	-0.217	0.047	0.298	0.021	0.000	0.921
Fat mass	-0.069	0.005	0.774	0.055	0.003	0.816	0.161	0.026	0.499	-0.122	0.015	0.609
Waist circumference	-0.735	0.540***	<0.001	-0.400	0.160	0.080	0.002	0.000	0.993	-0.603	0.363**	0.005
HbA1c	0.037	0.001	0.862	0.298	0.089	0.157	0.656	0.430***	<0.001	0.343	0.118	0.100
0' glucose	0.591	0.350**	0.002	0.322	0.104	0.125	0.283	0.080	0.181	0.214	0.046	0.315

120' glucose	0.693	0.480***	<0.001	0.852	0.725***	<0.001	0.491	0.241*	0.015	0.407	0.166*	0.048
HOMA-IR	0.200	0.040	0.348	0.219	0.048	0.304	0.479	0.230*	0.018	-0.257	0.066	0.255
O-DI	-0.167	0.028	0.445	0.017	0.000	0.939	0.437	0.191*	0.037	0.363	0.132	0.088
O-BCGS	-0.117	0.014	0.595	0.094	0.009	0.668	0.499	0.249*	0.015	0.358	0.128	0.086
GGI-DI	-0.280	0.079	0.195	-0.090	0.008	0.684	-0.041	0.002	0.853	-0.052	0.003	0.813
GGI-BCGS	-0.358	0.128	0.093	-0.157	0.025	0.474	-0.031	0.001	0.888	-0.116	0.013	0.600
eIGI	-0.149	0.022	0.487	0.137	0.019	0.524	0.537	0.288**	0.007	0.368	0.136	0.077
tIGI	-0.243	0.059	0.252	-0.188	0.036	0.378	-0.203	0.041	0.342	-0.222	0.049	0.298

Supplemental Table 3: Univariate predictive models of latest outcome variables

Univariate regression analysis data are given as βcoefficient, B, linear regression coefficient, R², and p; regression between pre-surgery/ 0-3M (% early change)/ 0-12/24M (% total change) [left column] and outcome at the latest timepoint (12M or 24M) [top row]; p values in **bold** indicate statistically significant variables; ***p<0.001, **p<0.01, or *p<0.05

Baseline	Remission status	P-REM vs F-REM			N-REM vs F-REM	
		LR p	OR	OR p	OR	OR p
Diabetes duration	0.005		1.8 (0.81-3.77)	0.153	1.9 (0.89-4.17)	0.099
Insulin use	0.006		1.21×10^{-9} (1.71×10^{-10} - 8.63×10^{-9})	<0.001	1.09×10^{-8} (1.09×10^{-8} - 1.09×10^{-8})	<0.001
HbA1c	0.279		1.42 (0.49 -4.13)	0.524	2.33 (0.710 - 7.63)	0.163
0' glucose	0.475		0.97(0.59-1.59)	0.92	1.24 (0.73 -2.11)	0.430
120' glucose	0.519		0.898 (0.66-1.22)	0.498	1.04 (0.74-1.46)	0.835
HOMA-IR	0.393		1.11 (0.93-1.35)	0.245	1.06 (0.86 - 1.29)	0.583
O-DI	0.036		300.69 (3.48×10^{-7} - 2.59×10^{11})	0.587	5.89×10^{-12} (1.19×10^{-32} - 2.9×10^9)	0.288
O-BCGS	0.008		3.02 (0.170 - 53.55)	0.451	0.009 (4.60×10^{-5} - 1.84)	0.083
GGI-DI	0.302		1.69×10^{-10} (9.22×10^{-27} - 3.12×10^6)	0.493	0.004 ($3.61 \times 3.56 \times 10^4$)	0.239
GGI-BCGS	0.035		9.44 (0.065- 1.37×10^3)	0.377	0.002 (1.23×10^{-7} -31.17)	0.207
eIGI	0.061		1.01 (0.99-1.02)	0.428	0.984 (0.96-1.01)	0.288
tIGI	0.012		1.01 (0.99-1.03)	0.586	0.925 (0.842-1.02)	0.106
Early change, 0-3M						
Body weight	0.118		1.29 (0.90-1.67)	0.188	1.37 (0.98-1.92)	0.070
Fat mass	0.343		1.03 (0.95-1.12)	0.498	1.07 (0.97-1.19)	0.185
Waist circumference	0.678		1.05 (0.943-1.17)	0.382	1.04(0.92-1.18)	0.514
HbA1c	0.051		1.03 (0.93-1.13)	0.066	1.12 (0.99-1.26)	0.621
0' glucose	0.074		1.03 (0.97-1.10)	0.309	1.07(1.00-1.14)	0.061
120' glucose	<0.001		1.11 (0.990-1.24)	0.073	1.24 (1.07-1.43)	0.004
HOMA-IR	0.014		1.02 (0.94-1.10)	0.676	1.09 (1.00-1.19)	0.056
O-DI	0.379		1.00 (0.99-1.00)	0.337	1.00 (0.99-1.00)	0.176

O-BCGS	0.260	1.00 (1.00-1.00)	0.324	1.00 (1.00-1.00)	0.753
GGI-DI	0.926	1.00 (1.00-1.00)	0.905	1.00 (1.00-1.00)	0.724
GGI-BCGS	0.226	1.00 (0.99-1.00)	0.686	1.00 (1.00-1.00)	0.410
eIGI	0.400	1.00 (1.00-1.00)	0.580	1.00 (1.00-1.00)	0.740
tIGI	0.073	1.00 (0.99-1.01)	0.576	0.98(0.96-1.00)	0.083
Total change (0-12/24M)					
Body weight	0.162	1.22 (0.98-1.26)	0.101	1.04 (0.92-1.17)	0.537
Fat mass	0.570	1.01 (0.93-1.09)	0.901	1.045 (0.94-1.16)	0.401
Waist circumference	0.170	1.042 (0.91-1.20)	0.565	1.05 (0.910-1.204)	0.521
HbA1c	0.831	1.02 (0.96-1.07)	0.613	1.02 (0.96-1.09)	0.565
0' glucose	0.113	1.03 (0.97-1.11)	0.330	1.06 (0.99-1.15)	0.099
120' glucose	<0.001	1.22 (1.00-1.49)	0.051	1.36 (1.09-1.70)	0.006
HOMA-IR	0.066	1.03 (0.92-1.15)	0.623	1.09 (0.964-1.22)	0.176
O-DI	0.262	1.00 (1.00-1.00)	0.293	1.00 (1.00-1.00)	0.892
O-BCGS	0.295	1.00 (1.00-1.00)	0.379	1.00 (1.00-1.00)	0.776
GGI-DI	0.426	1.00 (1.00-1.00)	0.820	1.00 (1.00-1.00)	0.415
GGI-BCGS	0.232	1.00 (1.00-1.00)	0.627	1.00 (1.00-1.00)	0.167
eIGI	0.466	1.00 (1.00-1.00)	0.968	1.00 (1.00-1.00)	0.618
tIGI	0.172	1.00 (0.99-1.01)	0.998	0.99 (0.97-1.01)	0.167

Supplemental Table 4: Univariate logistic regression LR=Likelihood ratio; OR=Odd's ratio; p values are from corresponding LR or OR tests by multinomial logistic regression to predict latest remission status; F-REM is reference category; Values in bold significantly predict remission status at p<0.05 or p<0.01 level by OR and/or LR.

Dependent	Predictors	Bivariate model		B	R ²	Overall p
		Variables entered	Variables removed			
HbA1c	Diabetes duration ¹ Insulin use ² Pre-surgery O-BCGS ³ Pre-surgery GGI-BCGS ⁴ Early change O-BCGS ⁵ Early change GGI-BCGS ⁶ Total change O-BCGS ⁷ Total change GGI-BCGS ⁸	1,3	3	0.412	0.170	0.041
		2,3	3	0.386	0.446	<0.001
		2,7	7	0.574 ² ; 0.339 ⁷	0.552	<0.001
		1,6	1	0.586	0.344	0.003
		1,5	--	0.405 ¹ ; 0.507 ⁵	0.427**	0.002
		2,5	--	0.576 ² ; 0.370 ⁵	0.575***	<0.001
		2,6	--	0.507 ² ; 0.360 ⁶	0.507***	<0.001
		1,7	--	0.426 ¹ ; 0.509 ⁷	0.428**	0.003

Supplemental Table 5A: Bivariate predictive model of longterm HbA1c

Bivariate regression analysis data are given as Beta coefficient, B, linear regression coefficient, R², and overall model significance, overall p; Different numbered superscripts Indicate predictor variables entered/removed in stepwise regression model. **Bold** p values indicate strongest predictors. *** linear regression is significant at the 0.001 level , **0.01 level; *0.05 level

Predictors	Bivariate model		Remission status LR P	P-REM vs F-REM		N-REM vs F-REM	
	variables entered	variables removed		OR	OR p	OR	OR p
Diabetes duration ¹ Insulin use ² Pre-surgery O-BCGS ³ Pre-surgery GGI-BCGS ⁴	1, 3	--	0.001	1.8 ¹ ; 24.1 ³	0.88-3.6 ¹ 0.14-4128.4 ³	1.81 ¹ ; 0.16 ³	0.88-3.71 ¹ ; 0.00-146.01 ³
	1,4	--	0.003	0.09 ¹ ; 584.8 ³	0.93-3.10 ¹ 0.06-5.3 x10e5 ⁴	1.16 ¹ ; 0.167 ⁴	0.88-3.01 ¹ ; 1.01e-6-2.7e4 ⁴
	2,3	2	0.003	7.56e-9 ² ; 4.78 ³	7.55e-9-7.55e-9 ² 0.191-119.36 ³	1.69e-9 ² ; 0.054 ³	1.79e-9-1.59e-8 ² ; 0.00-8.42 ³
	2,4	2	0.013	4.33e-9 ² ; 68.39 ⁴	4.33e-9-4.33e-9 ² 0.064-7.3e4 ⁴	1.31e-9 ² ; 0.557 ⁴	1.03e-10-1.67e-8 ² ; 01.01e-5-3.1e4 ⁴

Supplemental Table 5B: Bivariate logistic regression: prediction of diabetes remission

Different numbered superscripts indicate predictor variables entered/removed in multinomial logistic regression model; LR=Likelihood ratio; OR=Odd's ratio; p values are from LR or OR; F-REM is reference category; Values in **bold** significantly predict remission status at p<0.05 or p<0.01 level by LR tests.