The Role of β-Cell Function and Insulin Sensitivity in the Remission of Type 2 Diabetes after Gastric Bypass Surgery

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Context: Bariatric surgery can induce remission in a high proportion of severely obese patients with type 2 diabetes mellitus (T2DM).

Objective: Our objective was to investigate predictors and mechanisms of surgery-induced diabetes remission.

Patients and Setting: Forty-three morbidly obese subjects (body mass index = 45.6 ± 5.0 kg/m^2), 32 with T2DM and 11 nondiabetic [normal glucose tolerance (NGT)], participated at a clinical research center.

Intervention: Patients underwent Roux-en-Y gastric bypass.

Main Outcome Measures: Diabetes remission and β-cell function were evaluated.

Results: Subjects were tested before and 45 d and 1 yr after surgery. Weight decreased similarly in T2DM and NGT (−39 kg at 1 yr, $P < 0.0001$). Insulin sensitivity improved in both groups in proportion to the changes in body mass index but remained lower in T2DM than NGT (386 ± 91 *vs.* 479 ± 89 ml/min · m^2, $P < 0.01$). Based on glycosylated hemoglobin and oral glucose testing, diabetes had remitted in nine patients at 45 d and in an additional 16 at 1 yr. In T2DM, β-cell glucose sensitivity increased early after surgery but was no further improved and still abnormal at 1 yr [median, 48 (coefficient interval, 53) pmol/min · m^2 · mM *vs.* median, 100 (coefficient interval, 68) of NGT, $P < 0.001$]. Baseline β-cell glucose sensitivity was progressively worse in early remitters, late remitters, and nonremitters (median, 54[coefficient interval, 50] *vs.* median, 22[coefficient interval, 26] *vs.* median, 4[coefficient interval, 10] pmol/min · m^2 · mM) and, by logistic regression, was the only predictor of failure [odds ratio for bottom tertile = 7.9 (95% confidence interval = 1.2–51.9); $P = 0.03$].

Conclusions: In morbid obesity, Roux-en-Y gastric bypass causes rapid and profound metabolic adaptations; insulin sensitivity improves in proportion to the weight loss, and β-cell glucose sensitivity increases independently of weight loss. Over a period of 1 yr after surgery, diabetes remission depends on the starting degree of β-cell dysfunction. **(*J Clin Endocrinol Metab* 96: E1372–E1379, 2011)**

Dysfunction of β-cells and insulin resistance are the main pathophysiological defects responsible for the development of hyperglycemia (1). Both these defects predict incident diabetes in high-risk subjects (2). Insulin resistance *per se* is not sufficient to cause hyperglycemia; mild degrees of β-cell dysfunction, on the other hand, may not result in diabetic hyperglycemia in insulin-sensitive individuals. It is only when impaired β-cell function occurs in the background of insulin

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Abbreviations: BMI, Body mass index; HbA_{1c}, glycosylated hemoglobin; HDL, high-density lipoprotein; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; RYGB, Roux-en-Y gastric bypass; T2DM, type 2 diabetes mellitus.

resistance that plasma glucose levels begin to rise (as is the case of individuals with impaired glucose tolerance) (3).

It has generally been held that β-cell function is severely compromised already at the time the disease manifests itself and thereafter continues to decline linearly with time. Several studies, however, have documented the possibility that β-cell function may be restored, at least partially, in type 2 diabetes mellitus (T2DM) (4–6). Strong evidence to this effect comes from the following observations: 1) bariatric surgery in morbidly obese T2DM patients can restore euglycemia, the acute insulin response to glucose (7–9), and insulin sensitivity (10, 11); 2) recent studies have reported that diabetic subjects return to euglycemia and normal insulin levels within days after surgery, long before a significant weight loss has occurred (12). In a large meta-analysis, Roux-en-Y gastric bypass (RYGB) has been reported to be effective in improving glycemic control in 80% of T2DM patients (13). The underlying pathophysiological mechanisms are not yet well understood.

Because RYGB bypasses the foregut, it has been hypothesized that both insulin action and β-cell function are influenced by signals originating from the duodenum and proximal jejunum. This view is supported by studies showing major changes in the levels of gastrointestinal hormones involved in the regulation of glucose metabolism early after RYGB (14). More in general, caloric restriction, weight loss, and functional changes in the enteroinsular axis are all possible mechanisms (reviewed in Ref. 15). For example, Gumbs *et al.* (16) suggested that the improvement in glucose metabolism and insulin resistance after bariatric operations is due to decreased stimulation of the enteroinsular axis by the caloric restriction in the short term and to weight loss in the longer term. Pories *et al.* (17) proposed that an excessive stimulation of intestinal incretins in vulnerable individuals is the cause of T2DM and that the cure through surgery is related to the reduction of this overstimulation. On the other hand, Rubino and Gagner (18) have suggested the existence of intestinal factors, derived from excessive stimulation of the upper digestive tract, as the cause of a deficient incretin action.

Collectively, these observations clearly suggest that there is a large margin for β-cell recovery of function in type 2 diabetes and that different segments of the gut could participate differentially in such recovery.

In the present work, we assessed the role of improved insulin sensitivity and β-cell function in the remission of T2DM after RYGB and, by obtaining measurements early and later after surgery, which of the two defects is predictive of remission.

Materials and Methods

Subjects

The study group included 32 patients with T2DM (19 women and 13 men) and 11 nondiabetic subjects [normal glucose tolerance (NGT), 10 women and one man] who were wait-listed for laparoscopic RYGB. Diabetes was diagnosed according to the American Diabetes Association criteria (19). Insulin-taking patients whose age of diabetes onset was 40 yr or older, whose body mass index (BMI) was over 30 kg/m^2, and who were negative for the presence of islet autoantibodies were also considered to have T2DM. Antidiabetic treatment was insulin in seven patients (90 IU/d), oral antidiabetic agents in 22 (sulfonylurea plus metformin), and diet alone in three subjects. Exclusion criteria were 1) medical conditions requiring acute hospitalization, 2) blindness, and 3) severe medical conditions (liver cirrhosis, end-stage renal failure, malignancy, connective tissue diseases, or endocrine diseases such as hypo- or hyperthyroidism) or illnesses such as chronic congestive heart failure, recent myocardial infarction or stroke, or unstable angina pectoris.

The protocol was approved by the local ethics committee, and all patients signed a written consent form before the study.

Design

After screening, patients were asked to attend our Clinical Research Unit for the baseline study 1 month before surgery. Two days before surgery, patients were admitted to our ward, where they were readmitted 3 d after surgery for another 6 d to optimize antidiabetic treatment. On the day of surgery, patients with fasting plasma glucose concentrations over 8.0 mmol/liter were started on an insulin infusion to maintain plasma glucose between 6.0 and 10.0 mmol/liter during surgery and for the 4 following days, until they resumed eating. After surgery, the metabolic study was repeated 45 d and 12 months later at the Clinical Research Unit. After surgery, diabetes remission was defined as glycosylated hemoglobin (HbA_{1c}) below 6.5%, fasting glucose below 7.0 mmol/liter, and 2-h glucose below 11.1 mmol/liter on the oral glucose tolerance test (OGTT) without antidiabetic treatment.

Protocol

For the metabolic study, all subjects were instructed not to exercise for 48 h before study and were examined in the morning after an overnight (12–14 h) fast. Peripheral blood samples were obtained for determination of the routine blood chemistry and lipid profile, plasma glucose, insulin, C-peptide, and HbA_{1c} concentrations. The diabetic patients on oral antidiabetic agents were asked to stop them 48–72 h before the study; in those on insulin, injections were discontinued 16 h before the metabolic study (patients on bedtime glargine had been switched to neutral protamine Hagedorn 2 d before the study). Height, weight, and systolic and diastolic blood pressure were measured and recorded. The metabolic study consisted of a frequently sampled OGTT. After an overnight (12 h) fast, blood samples were collected through an indwelling cannula to measure fasting plasma glucose, insulin, and C-peptide. After ingestion of 75 g glucose in aqueous solution, venous blood was sampled at 10, 20, 30, 45, 60, 90, 120, 150, and 180 min for glucose, insulin, and C-peptide assay.

Laparoscopic RYGB

After identification of the Treitz ligament, the jejunum was transected at 120 cm from the ligament of Treitz and an enteroenterostomy was performed using a 45-mm linear stapler at 150 cm on the alimentary limb. A subcardial gastric pouch with a 30- to 50-ml capacity was created on a nasogastric balloon catheter guide by sectioning the stomach with a linear stapler, and a 2.5- to 3-cm long gastrojejunal anastomosis was performed by a hand-sewn technique (20).

Methods

Plasma glucose concentration was measured on a Beckman Glucose Analyzer 2 (Beckman, Fullerton, CA). Fasting concentrations of serum total cholesterol low-density lipoprotein cholesterol, and high-density lipoprotein (HDL)-cholesterol were measured by standard techniques (Synchron CX4; Beckman Instruments, Inc., Brea, CA). Plasma insulin and C-peptide were measured by Cobas e411 (Roche Diagnostics S.p.A., Milan, Italy).

Modeling

Insulin sensitivity and β-cell function parameters were derived from mathematical modeling of the plasma glucose, insulin, and C-peptide concentrations measured during the frequently sampled OGTT, as previously described (21). In brief, insulin sensitivity was calculated as the oral glucose insulin sensitivity index, which estimates plasma glucose clearance rate (in millimeters per minute per square meter) at a level of hyperinsulinemia in the range of that achieved during a standard (240 pmol/min · m^2) euglycemic-hyperinsulinemic clamp, against which this index has been validated in subjects with NGT, impaired glucose tolerance, or overt diabetes (22).

The β-cell function model consists of three blocks: 1) a model for fitting the glucose concentration profile, the purpose of which is to smooth and interpolate plasma glucose concentrations; 2) a model describing the dependence of insulin (or C-peptide) secretion on glucose concentration; and 3) a model of C-peptide kinetics, *i.e.* the two-exponential model proposed by Van Cauter *et al.* (23), in which the model parameters are individually adjusted to the subject's anthropometric data. In particular, with regard to the insulin secretion block (no. 2), the relationship between insulin release and plasma glucose concentrations is modeled as the sum of two components. 1) The first component is the relationship between insulin secretion and glucose concentration, *i.e.* a dose-response function. The dose-response function is modulated by a time-varying factor, expressing a potentiation effect on insulin secretion (22). The dose-response function is a parameterized function of glucose concentration that can be either quasilinear or convex, depending on the parameters (24). The mean slope of the dose-response function is taken to represent β-cell glucose sensitivity (β-GS, in picomoles per minute per square meter per millimolar). 2) The second insulin secretion component represents a dynamic dependence of insulin secretion on the rate of change of glucose concentration, *i.e.* rate sensitivity. Total insulin secretion is the sum of the two components described above.

Statistical analysis

Results are expressed as mean ± SD or median (interquartile range) for variables with normal or skewed distribution, respectively. Group differences were compared by the χ^2 test for categorical variables, by the Mann-Whitney *U* test for continuous variables and by Wilcoxon signed rank test for paired data. Analysis of changes over time (before, early, and late after surgery) in the two subject groups (NGT and T2DM) was carried out by ANOVA for repeated measures; for this test, parameters with a skewed distribution were log-transformed. The output of this ANOVA model is a *P* value for the time factor (*i.e.* overall changes over time), a *p* value for the group (*i.e.* between-group differences), and a *P* value for the time × group interaction (*i.e.* differential changes between groups over time). A P value <0.05 was considered to be significant.

TABLE 1. Clinical and metabolic characteristics of the study subjects before (Pre), 45 d (Post-1), and 1 yr (Post-2) after surgery (RYGB)

	NGT			T2DM		
	Pre	**Post-1**	**Post-2**	**Pre**	**Post-1**	**Post-2**
Subjects	11	11	11	32	32	32
BMI (kg/m^2)[a]	46.3 ± 7.4	39.7 ± 7.2	30.5 ± 5.2	45.4 ± 5.5	39.9 ± 5.9	31.8 ± 5.5
HbA_{1c} (%)[a,b,c]	5.5 ± 0.5	5.4 ± 0.4	5.3 ± 0.4	7.6 ± 2.1	6.8 ± 1.0	5.9 ± 0.7
Fasting glucose (mg/dl)[a,b,c]	96 ± 11	89 ± 7	83 ± 6	145 ± 38	122 ± 36	99 ± 30
Fasting insulin (μU/ml)[a]	16 (8)	12 (10)	7 (4)	21 (19)	14 (9)	12 (8)
2-h glucose (mg/dl)[a,b,c]	131 ± 19	105 ± 19	76 ± 42	270 ± 70	190 ± 82	149 ± 77
2-h insulin (μU/ml)[a]	91 (44)	44 (44)	22 (33)	61 (111)	44 (70)	38 (27)
Blood pressure (mm Hg)						
Systolic[a]	134 ± 19	117 ± 9	121 ± 9	132 ± 15	129 ± 13	134 ± 20
Diastolic[a]	82 ± 15	75 ± 5	78 ± 7	86 ± 7	83 ± 8	81 ± 10
Triglycerides (mg/dl)[a,b]	118 (28)	101 (39)	90 (45)	179 (113)	165 (110)	125 (48)
Total cholesterol (mg/dl)[a]	193 ± 19	180 ± 22	177 ± 25	195 ± 21	183 ± 33	176 ± 28
HDL-cholesterol (mg/dl)[a]	44 ± 10	43 ± 9	48 ± 11	40 ± 8	37 ± 8	48 ± 10

Numbers in parentheses indicate coefficient interval and *numbers outside parentheses* indicate median.

[a] $P < 0.05$ for the time factor.

[b] $P < 0.05$ for the group factor (NGT *vs.* T2DM).

[c] $P < 0.05$ for the time × group interaction.

TABLE 2. Metabolic parameters of the study subjects before (Pre), 45 d (Post-1), and 1 yr (Post-2) after surgery (RYGB)

	NGT			T2DM		
	Pre	**Post-1**	**Post-2**	**Pre**	**Post-1**	**Post-2**
Insulin sensitivity (ml/min · m^2)[a,b]	358 ± 46	406 ± 50	479 ± 89	263 ± 33	308 ± 54	386 ± 91
Fasting insulin secretion (pmol/min · m^2)[a]	99 (86)	85 (92)	62 (33)	141 (73)	112 (50)	79 (33)
Total insulin output (nmol/m^2)	58 (35)	64 (50)	49 (27)	44 (47)	60 (39)	52 (45)
β-cell glucose sensitivity (pmol/min · m^2 · mM)[a,b]	62 (18)	115 (52)	100 (68)	22 (30)	44 (58)	48 (53)
Rate sensitivity (nmol/m^2 · mM)[a,b]	0.94 (1.15)	1.88 (1.90)	1.40 (1.41)	0.27 (0.57)	0.72 (0.91)	0.85 (0.71)
Potentiation factor[a]	1.25 (0.70)	1.01 (0.72)	1.34 (1.22)	1.02 (0.24)	1.15 (0.56)	1.13 (0.62)

Numbers in parentheses indicate coefficient intervals and *numbers outside parentheses* indicate median.

[a] $P < 0.05$ for the time factor.

[b] $P < 0.05$ for the group factor (NGT *vs.* T2DM).

Results

Baseline anthropometric and metabolic parameters in diabetic and nondiabetic subjects

Degree of obesity was similar in T2DM and NGT subjects, but T2DM patients were older (52 ± 8 *vs.* 39 ± 8 yr, $P < 0.001$), and had higher baseline HbA_{1c}, fasting and 2-h plasma glucose, and serum triglyceride levels than NGT subjects (Table 1). Baseline insulin sensitivity, β-cell glucose sensitivity, and rate sensitivity were significantly worse in T2DM than NGT, whereas fasting and total insulin secretion and the potentiation factor were similar between the two groups (Table 2).

Effects of RYGB in diabetic and nondiabetic subjects

With surgery, BMI decreased similarly in both groups. At 45 d after surgery, weight loss averaged 18 kg (range 9–25) in NGT and 15 kg (range 5–42) in T2DM; at 1 yr, the corresponding values were 44 kg (range 26–85) in NGT and 37 kg (range 14–74) in T2DM. Fasting and 2-h plasma insulin concentrations, systolic and diastolic blood pressure, total cholesterol, and triglycerides concentrations all decreased with surgery, whereas HDL-cholesterol was significantly increased. Glycemic control, as indexed by HbA_{1c} and fasting and 2-h plasma glucose levels, improved significantly more in T2DM than NGT (Table 1).

Insulin sensitivity was improved both early and late after surgery in both NGT and T2DM ($P = 0.01$ or less); in the latter, however, it remained lower than in NGT throughout the follow-up ($P < 0.0001$ and $P < 0.01$ at 45 days and 1 yr, respectively) (Table 2). In both groups, insulin sensitivity closely tracked with BMI (Fig. 1). β-Cell glucose sensitivity showed a marked improvement in both groups, but the values at 1 yr were not different from those at 45 d, and in the T2DM patients, they remained significantly lower than in NGT subjects ($P < 0.001$ at both 45 d and 1 yr). In both groups, β-cell glucose sensitivity closely tracked with 2-h plasma glucose concentrations (Fig. 2). The pattern of changes of rate sensitivity was similar to that of glucose sensitivity, whereas the potentiation factor was greater at 1 yr than baseline only in the T2DM ($P = 0.03$). Fasting insulin secretion declined with time after surgery in both groups, whereas total insulin output did not change (Table 2).

Diabetes remission

By defining remission as HbA_{1c} below 6.5%, fasting glucose <7.0 mmol/liter, and 2-h glucose below 11.1 mmol/liter off antidiabetic treatment, diabetes had remitted in nine of the 32 patients already at 45 d after surgery and in another 16 patients at 1 yr; this left seven patients in whom diabetes was improved but not in remission even at 1 yr. Neither age nor BMI (at baseline or after surgery) distinguished the nonremitters from the remitters; in contrast, baseline HbA_{1c}, fasting and 2-h plasma glucose levels, insulin sensitivity, β-cell glucose sensitivity, and rate sensitivity were all progressively worse from early remit-

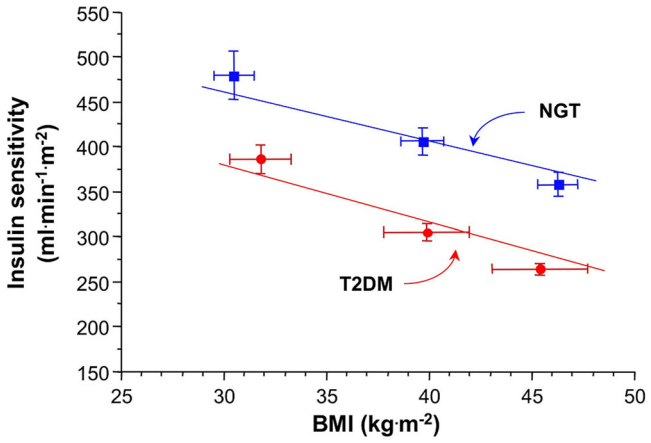

FIG. 1. Consensual changes in BMI and insulin sensitivity in nondiabetic (NGT) and diabetic patients (T2DM), before and 45 d and 1 yr after RYGB surgery. Plots are mean ± SEM. The regression equations are y = 552x 6.0 × (r = 0.58; $P < 0.0001$) for T2DM and y = 620 − 5.3x (r = 0.60; $P = 0.0002$) for NGT.

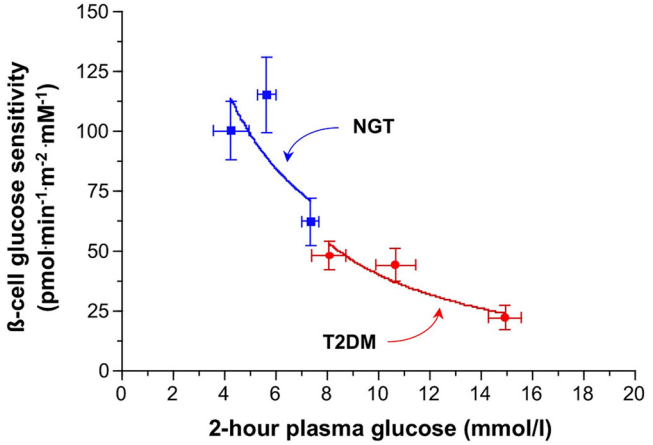

FIG. 2. Consensual changes in 2-h plasma glucose concentrations and β-cell glucose sensitivity in nondiabetic (NGT) and diabetic patients (T2DM), before and 45 d and 1 yr after RYGB surgery. Plots are mean ± SEM.

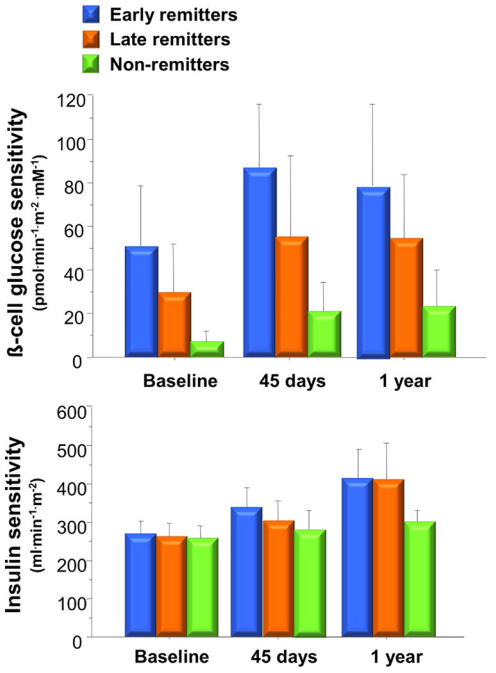

FIG. 3. β-Cell glucose sensitivity and insulin sensitivity in early diabetes remitters (45 d), late remitters (1 yr), and nonremitters. Plots are mean ± SEM. By two-way ANOVA for repeated measures, the *P* value for β-cell glucose sensitivity is <0.0005 for remission status and <0.0001 for time. For insulin sensitivity, the *P* value for the interaction remission × time is <0.02.

ters to late remitters to nonremitters (Table 3). With regard to antidiabetic treatment, all seven subjects on diet treatment remitted at 45 d; of the 22 patients on oral agents, three remitted at 45 d and 14 remitted at 1 yr; and of the three patients on insulin only, one remitted at 1 yr and two were nonremitters. Thus, antidiabetic treatment was weakly related to remission rate ($\chi^2 = 5.5$; $P = 0.06$). Furthermore, although all metabolic parameters, except total insulin output, showed the expected improvement after surgery, the extent of the improvement was significantly less in nonremitters compared with remitters for fasting glucose (Table 3), insulin sensitivity, and β-cell glucose sensitivity (Fig. 3).

In univariate logistic analysis of the data from the T2DM group, 2-h plasma glucose levels [odds ratio for 1 SD = 5.7 (95% confidence interval = 1.5–21.7); $P = 0.01$] and β-cell glucose sensitivity [odds ratio for values in the bottom tertile (*i.e.* <12.5 pmol/min · m^2 · mM) = 7.9 (95% confidence interval = 1.2–51.9); $P = 0.03$] predicted failure of diabetes remission. In bivariate regression, log-transformed glucose sensitivity was superior to 2-h plasma glucose in predicting persistence of diabetes at 1 yr after surgery. Diabetes duration, antidiabetic therapy, and baseline HbA_{1c} were not predictors of remission. In a

TABLE 3. Clinical and metabolic characteristics of diabetic subjects according to diabetes remission before (Pre), 45 d (Post-1), and 1 yr (Post-2) after surgery (RYGB)

	Early remission			Late remission			Nonremission		
	Pre	Post-1	Post-2	Pre	Post-1	Post-2	Pre	Post-1	Post-2
Subjects	9	9	9	16	16	16	7	7	7
Age (yr)	49 ± 8			54 ± 8			53 ± 8		
Diabetes duration (yr)[b]	4.2 ± 3.3			8.9 ± 6.0			10.1 ± 5.7		
BMI (kg/m^2)[a]	44.2 ± 5.8	38.8 ± 7.1	29.8 ± 5.3	45.7 ± 5.3	39.7 ± 5.0	31.3 ± 4.5	46.5 ± 6.0	41.7 ± 6.7	35.6 ± 6.9
HbA_{1c} (%)[a,b]	6.2 ± 0.2	5.8 ± 0.3	5.4 ± 0.3	7.9 ± 1.9	7.0 ± 0.9	5.8 ± 0.5	8.9 ± 2.3	8.0 ± 1.0	6.9 ± 0.9
Fasting glucose (mmol/liter)[a,b,c]	121 ± 22	103 ± 11	92 ± 10	149 ± 35	118 ± 19	85 ± 11	170 ± 45	167 ± 52	141 ± 43
2-h glucose (mmol/liter)[a,b]	220 ± 52	121 ± 31	100 ± 28	265 ± 46	192 ± 53	128 ± 32	340 ± 68	286 ± 79	244 ± 65
Fasting insulin (pmol/liter)[a]	137 (127)	110 (57)	51 (44)	134 (94)	90 (87)	47 (18)	164 (112)	103 (48)	80 (57)
2-h insulin (pmol/liter)[a,c]	1040 (864)	748 (388)	347 (299)	911 (639)	612 (592)	320 (122)	1115 (762)	700 (326)	544 (388)
Insulin sensitivity (ml/min · m^2)[a,b,c]	269 ± 32	337 ± 54	414 ± 78	264 ± 34	303 ± 52	408 ± 97	255 ± 36	268 ± 33	301 ± 30
Fasting secretion (pmol/min · m^2)[a]	172 (60)	112 (33)	87 (32)	128 (61)	111 (79)	74 (38)	110 (83)	135 (32)	85 (41)
Total output ($nmol/m^2$)	80 (32)	64 (34)	48 (33)	43 (43)	63 (43)	56 (60)	31 (21)	50 (27)	42 (33)
Glucose sensitivity (pmol/min · m^2 · mM)[a,b]	54 (50)	78 (49)	59 (54)	22 (26)	42 (60)	54 (46)	4 (10)	14 (23)	16 (30)
Rate sensitivity ($nmol/m^2$ · mM)[a,b]	0.51 (1.11)	1.04 (1.49)	1.05 (0.63)	0.27 (0.52)	0.67 (0.92)	0.90 (0.77)	0.04 (0.30)	0.14 (0.50)	0.34 (075)
Potentiation factor[a]	1.11 (0.25)	1.41 (1.14)	1.73 (1.24)	1.02 (0.24)	1.10 (0.46)	1.12 (0.50)	1.02 (0.18)	1.01 (0.50)	1.14 (0.21)

Numbers in parentheses indicate coefficient interval and *numbers outside parentheses* indicate median.

[a] $P < 0.05$ for the time factor.

[b] $P < 0.05$ for the group factor (early remission, late remission, or nonremission).

[c] $P < 0.05$ for the time × group interaction.

multivariate model including diabetes duration and baseline HbA_{1c}, only glucose sensitivity was a significant predictor of remission.

Discussion

The major findings of the present study are that in morbidly obese individuals, 1) for the same degree of overweight, T2DM patients had worse baseline insulin sensitivity and β-cell glucose sensitivity (Table 2); 2) in both nondiabetic and T2DM patients, insulin sensitivity improved essentially in proportion to the surgery-induced decrement in BMI (Fig. 1); 3) in both nondiabetic and T2DM patients, β-cell glucose sensitivity improved relatively early after surgery and then leveled off in tandem with, and over a continuum of, plasma glucose concentrations (Fig. 2); 4) on average, the increase in β-cell glucose sensitivity in T2DM patients remained well below that of nondiabetic patients; and 5) β-cell glucose sensitivity, not insulin sensitivity, was the only predictor of remission and time of remission of diabetes (Fig. 3).

With regard to the first result, it is well documented that a variable mix of insulin resistance and β-cell dysfunction is characteristic of T2DM (1), and that β-cell dysfunction tends to progressively decline over time even with treatment (25, 26). The current results document that, although baseline insulin sensitivity is similarly depressed in remitters and nonremitters, β-cell glucose sensitivity and rate sensitivity are progressively worse at baseline, and fail to improve, in nonremitters as compared with remitters (Fig. 3), thereby emerging as a strong predictor of remission. Importantly, in our T2DM patients, remission was independent of the amount of weight lost, which was comparable across the three groups. Thus, if insulin resistance is a close concomitant of morbid obesity and benefits from weight loss, degree and time course of reversal of hyperglycemia are critically dependent on β-cell status. The worse initial degree of β-cell dysfunction, especially glucose sensing, the lower the chances that it may be reversed by intervention. This paradigm very probably applies to any intervention, including lifestyle and pharmacological management (25), but bariatric surgery amplifies the impact of residual β-cell function by drastically enhancing insulin sensitivity. The initial degree of impairment of β-cell function can be the result of a longer known duration of diabetes, higher exposure to glucose toxicity (*e.g.* Table 3), or stronger genetic drive (or combinations thereof) (27, 28). Of note in this regard is that β-cell function was not fully restored (*i.e.* to the level observed in NGT patients) even in remitters and may therefore signal the possibility of diabetes relapse. In fact, in remitters, there was little further improvement between 45 d and 1 yr after surgery (Fig. 3). Continued follow-up of our patient cohort will assess the rate of durable remission when diabetes remission is defined as stringently as was done in this work.

The present results also speak to the specific mechanisms by which RYGB improves glucose metabolism. In obese subjects with T2DM, gastric banding has been shown to enhance insulin action in proportion to weight loss (29). On the other hand, calorie restriction *per se* may contribute to the improvement in insulin sensitivity in obese diabetic subjects (30). Unlike some previous studies (31) but in accord with others (32), we do not find evidence that RYGB affects insulin sensitivity by weight-independent mechanisms (Fig. 1). Although it remains theoretically possible that bypassing the duodenum and proximal jejunum releases putative inhibitors of insulin action (16), the current results indicate that their effects must be at best minor in humans. On the other hand, the relation of insulin sensitivity to BMI likely reflects the dependency of insulin action on im triglyceride content. In fact, several studies have reported an inverse relationship between insulin sensitivity and im fat content (33). In a rat model of diet-induced obesity and insulin resistance, acute dietary lipid withdrawal ameliorated muscle insulin resistance (34). Furthermore, in morbidly obese patients undergoing biliopancreatic diversion, the increase in insulin sensitivity was closely associated with depletion of intramyocellular triglycerides (10).

With regard to β-cell function, to our knowledge, there are no data in the literature showing how β-cell glucose sensitivity on the OGTT changes early after RYGB, and the present data are not directly comparable with those obtained in previous studies because of different surgical techniques (variants of vertical banded gastroplasty) and stimulation tests (arginine and iv glucose infusions) (35, 36). The rapid amelioration of β-cell dysfunction seen in our T2DM remitters has multiple potential explanations. Calorie restriction clearly plays some role, because RYGB typically imposes a daily intake of roughly 800 kcal (at least early after surgery). The ability of calorie restriction (or fasting) to quickly lower plasma glucose and insulin concentration is well documented (37). In the present studies, a doubling of β-cell glucose sensitivity occurred also in the NGT group and was paralleled by a marked drop in fasting insulin secretion rates (Table 2). Another factor is the removal of glucose toxicity, which *per se* can enhance glucose sensing (38). In fact, the close quantitative and temporal association between glucose levels and β-cell glucose sensing (Fig. 2) is a two-way cause-effect relationship; glucose sensing is the major determinant of plasma glucose concentrations during acute stimulation,

and chronic hyperglycemia is toxic for pancreatic islets (39). A further mechanism is the abatement of insulin resistance itself, which at the very least decreases the workload of β-cells. Finally, the surge in incretin hormones that follows RYGB, which has been well documented in several studies (18), can specifically potentiate β-cell function. Indeed, we have previously shown that glucose-stimulated glucagon-like peptide-1 release is positively associated with β-cell glucose sensitivity in both nondiabetic and diabetic subjects (40). On these bases, our data suggest that on a background of better β-cell function, the improvement in β-cell glucose sensitivity after RYGB, represents the major determinant in the remission of T2DM.

In summary, RYGB causes rapid and profound metabolic adaptations, some more dependent on the weight loss (insulin sensitivity) and some more related to complex influences on β-cell function. Over a period of 1 yr after surgery, diabetes remission may occur in three quarters of T2DM patients depending on the starting degree of β-cell dysfunction.

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