Determinants of Diabetes Remission and Glycemic Control After Bariatric Surgery

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OBJECTIVE

Eligibility criteria for bariatric surgery in diabetes include BMI ≥35 kg/m^2 and poorly controlled glycemia. However, BMI does not predict diabetes remission, and thus, predictors need to be identified.

RESEARCH DESIGN AND METHODS

Seven hundred twenty-seven patients were included in a database merged from the Swedish Obese Subjects (SOS) study and two randomized controlled studies, with 415 surgical and 312 medical patients in total. Bariatric operations were divided into gastric only (GO) and gastric plus diversion (GD).

RESULTS

Sixty-four percent of patients in the surgical arm and 15.0% in the medical arm experienced diabetes remission (P < 0.001). GO yielded 60% remission, and GD yielded 76% remission. The best predictors of diabetes remission were lower baseline glycemia and shorter diabetes duration. However, when operation type was considered, GD predicted a higher likelihood of remission and greater weight loss. Patients in remission (responders) lost more weight (25% vs. 17%) and waist circumference (18% vs. 13%) and experienced better insulin sensitivity than nonresponders.

CONCLUSIONS

Surgery is more effective than medical treatment in achieving diabetes remission and tighter glycemic control. Shorter diabetes duration, lower fasting glycemia before surgery, and GD versus GO procedures independently predict higher rates of remission, whereas baseline HbA$_{1c}$ and waist circumference predict improved glycemic control. The results show the advantage of an early operation together with better controlled glycemia on diabetes remission independently of BMI.

The prospective, controlled Swedish Obese Subjects (SOS) study showed that the short-term rate of remission of diabetes after bariatric surgery is 72% compared with 21% in subjects treated with conventional weight loss methods (1). Randomized controlled studies have revealed diabetes remission rates between 37% and 42% (2) to 73% (3), 24% and 38% (4), and 75% and 95% (5), depending on the criteria used to define diabetes remission and baseline patient characteristics, choice of surgical therapy, and duration of follow-up (1–3 years). Unfortunately, such differences in diabetes remission criteria obscure important questions regarding the determinants of diabetes remission, which in turn affect eligibility criteria for patient selection for bariatric surgery.

Historically, only subjects with BMI ≥35 kg/m^2 in the presence of uncontrolled diabetes were considered as potential candidates for bariatric and metabolic

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surgery (6). The International Diabetes Federation statement of 2011 (7) made advances on this criterion, stating that surgery should be prioritized for patients with type 2 diabetes (T2D) and BMI >40 kg/m^2 and indicated for patients with BMI 35–40 kg/m^2 and poorly controlled diabetes (HbA_{1c} >7.5%) despite fully optimized conventional therapy. The statement also made provisions for patients with BMI 30–35 kg/m^2, stating that these patients should be considered for surgery if the target HbA_{1c} (<7.5%) is not achieved with conventional medical therapy and lifestyle modification attempts and if other obesity-related concerns are present. Therefore, according to current best practice, in the presence of poorly controlled diabetes, BMI appears to represent the only criterion for bariatric surgery eligibility. However, no direct evidence demonstrates that BMI is a predictor of diabetes remission after bariatric surgery. In fact, the use of BMI as a selection condition for bariatric surgery for T2D treatment in obese patients (BMI >34 kg/m^2) has been shown not to predict outcome (5), thus challenging the strict BMI criteria. Indeed, a meta-analysis (8) investigating the risks and benefits associated with surgical and medical therapies for treating diabetes or impaired glucose tolerance in patients with BMI 30–35 kg/m^2 showed that surgery is more effective than medical therapy.

The present investigation was designed primarily to calculate the 2-year diabetes remission rate after bariatric surgery compared with medical treatment and to assess the predictors of remission. Diabetes remission criteria were standardized as fasting plasma glucose <5.6 mmol/L without pharmacological treatment. We also examine the proportion of surgical and medical patients who achieved tight glycemic control at 2 years.

RESEARCH DESIGN AND METHODS

The database from the SOS study (1) was merged with databases of two randomized controlled studies (3,5), yielding a combined group of patients with T2D who underwent conventional medical therapy and a combined group who underwent bariatric surgery. The lifestyle interventions in the medical arm differed among the three centers involved in the study. For the SOS study, no attempt to standardize the recommendations among the Swedish recruiting centers was made. In the study by Dixon et al. (3), patients were asked to reduce global energy intake, particularly of fat to <30% (including saturated fats), and encouraged to consume low–glycemic index and high-fiber foods. Physical activity of 10,000 steps/day and 200 min/week of structured activity was also encouraged, including moderate-intensity aerobic activity and resistance exercise. Suggestions similar to those adopted in the study by Dixon et al. were made in the study by Mingrone et al. (5).

Baseline and 2-year characteristics of subjects in the medical and surgical arms are summarized in Table 1. To harmonize the results from the three studies, diabetes remission was defined as normal fasting glycemia (<5.6 mmol/L) in the absence of any antidiabetic medication. Hereafter, patients with diabetes remission are identified as responders.

From the available information about medication usage, a categorical variable with three levels (0 = no medication, 1 = only oral hypoglycemic agents, 2 = insulin or insulin plus oral hypoglycemic agents) was built. The variables analyzed were sex, age, weight, BMI, waist circumference, diabetes duration, type of antidiabetic medication, fasting concentrations of glucose and insulin, HOMA of insulin resistance (IR), total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and systolic blood pressure (SBP) and diastolic blood pressure (DBP). HbA_{1c} was also available from the study by Dixon et al. (3) and the study by Mingrone et al. (5).

Overall, the three studies pooled included four different surgical techniques: vertical banded gastroplasty (VBG), gastric banding (GB, either adjustable or nonadjustable), Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion (BPD). We compared the percent variation from baseline at 2 years of weight, BMI, and waist circumference (Supplementary Table 1). For these variables, post hoc comparisons after ANOVA with two between-factor components (responders vs. nonresponders and surgical technique with four levels [Supplementary Table 2]) showed no significant differences between VBG and GB, the two procedures with purely gastric components (gastric only [GO]), and between RYGB and BPD, the two techniques that divert gastric content distally into the small intestine (gastric with diversion [GD]). Consequently, the patients were divided into two surgical therapy groups, and analyses were performed comparing the two different macrotechniques GO and GD.

To predict diabetes remission, a logistic model was used. Each aforementioned variable was initially entered in a univariate logistic regression to study its ability to independently predict diabetes remission. Only predictors significantly associated with remission in the univariate analysis were entered into a multivariate model, and their ability to independently predict remission was assessed by a stepwise elimination method.

The percentage of patients attaining fasting glycemia <7 mmol/L or HbA_{1c} <7% at 2 years was calculated as representing those achieving tight glycemic control. Pearson coefficients were used to study correlations among variables. Dependence of continuous variables (changes in glycemia, HbA_{1c}, and HOMA-IR) on predictors was studied by multivariable linear models. For each variable at baseline and for percent change at 2 years, ANOVAs (with the two aforementioned between-factor comparisons) were performed. Receiver operating characteristic (ROC) analyses were used to identify the most appropriate cutoffs of the variables of interest as predictors of diabetes remission at 2 years. Multivariate ROC analysis was also performed to study the predictive capability, in terms of area under the curve (AUC), of the best variable combination in estimating the probability of remission, for which the best cutoff value is also reported (lr.η).

RESULTS

Sample Description

In total, 727 patients with T2D were analyzed, 415 of whom were surgically treated. There were 227 cases of VBG, 91 of GB, 77 of RYGB, and 20 of BPD. The dropout rate at 2 years was 10.4% in the surgical group and 19.9% in the medical group. The average diabetes duration was 0.7 ± 1.9, 4.1 ± 3.3, and 9.8 ± 6.5 years in patients not taking medications, taking oral agents only, or taking insulin or insulin plus oral agents, respectively.

Comparison Between Medical and Surgical Patients

In the medical arm, 15% of the patients achieved diabetes remission compared

Table 1—Variables at baseline and after 2 years and percent change in the medical treatment and surgical arms independent of the surgical technique used

	Baseline					2 years					Percent change				
	Medical treatment		Surgery			Medical treatment		Surgery			Medical treatment		Surgery		
	n	Mean ± SD	*n*	Mean ± SD	*P* value	*n*	Mean ± SD	*n*	Mean ± SD	*P* value	*n*	Mean ± SD	*n*	Mean ± SD	*P* value
Age (years)	312	49.7 ± 6.9	410	48.0 ± 6.4	<0.001	—	—	—	—	—	—	—	—	—	—
Weight (kg)	312	116.6 ± 17.8	415	122.9 ± 20.1	<0.001	251	113.7 ± 18.4	373	94.3 ± 17.6	<0.001	251	−2.5 ± 6.5	373	−22.4 ± 10.8	<0.001
Waist circumference (cm)	312	122.3 ± 11.2	413	127.8 ± 13.0	<0.001	251	119.8 ± 10.9	371	106.7 ± 14.3	<0.001	251	−1.3 ± 11.9	369	−16.0 ± 9.1	<0.001
BMI (kg/m^2)	312	40.1 ± 4.9	415	42.0 ± 5.0	<0.001	251	39.0 ± 4.9	373	32.4 ± 5.0	<0.001	251	−2.5 ± 6.5	373	−22.4 ± 10.8	<0.001
Glycemia (mmol/L)	312	8.8 ± 2.8	414	8.7 ± 2.7	NS	250	8.2 ± 2.9	372	5.2 ± 2.0	<0.001	250	−1.2 ± 33.9	371	−36.4 ± 23.1	<0.001
Insulinemia (mU/L)	311	25.1 ± 17.3	410	27.4 ± 18.3	NS	250	21.9 ± 14.8	372	12.4 ± 7.7	<0.001	249	1.3 ± 51.6	368	−47.4 ± 31.0	<0.001
HbA_{1c} (%)	50	8.0 ± 1.4	70	8.3 ± 1.5	NS	44	7.2 ± 1.0	67	5.8 ± 1.0	<0.001	44	−6.0 ± 14.3	67	−29.3 ± 16.8	<0.001
HOMA-IR	311	9.7 ± 7.5	409	10.6 ± 7.6	NS	250	8.0 ± 5.8	372	3.1 ± 3.1	<0.001	249	−0.1 ± 56.6	367	−64.9 ± 29.5	<0.001
SBP (mmHg)	282	144.4 ± 20.4	384	150.6 ± 20.0	<0.001	225	142.0 ± 17.6	341	139.7 ± 21.6	NS	225	−1.6 ± 12.0	340	−6.8 ± 13.7	<0.001
DBP (mmHg)	282	87.8 ± 12.0	384	92.0 ± 11.5	<0.001	225	85.3 ± 9.6	341	84.7 ± 11.0	NS	225	−2.1 ± 11.7	340	−7.3 ± 11.9	<0.001
HDL cholesterol (mmol/L)	293	1.2 ± 0.3	390	1.2 ± 0.3	NS	239	1.3 ± 0.3	364	1.5 ± 0.4	<0.001	230	4.5 ± 15.4	344	25.6 ± 81.0	<0.001
Total cholesterol (mmol/L)	312	5.7 ± 1.2	414	5.8 ± 1.2	NS	250	5.4 ± 1.2	372	5.4 ± 1.3	NS	250	−1.7 ± 15.4	371	−5.0 ± 20.4	0.030
Triglycerides (mmol/L)	312	2.9 ± 2.9	414	2.8 ± 2.1	NS	249	2.4 ± 1.5	372	1.7 ± 1.0	<0.001	249	0.6 ± 44.2	371	−29.7 ± 32.7	<0.001
LDL cholesterol (mmol/L)	293	3.2 ± 1.2	390	3.3 ± 1.0	NS	239	3.1 ± 0.9	364	3.2 ± 1.1	NS	230	−2.3 ± 23.7	344	−1.5 ± 36.9	NS
Diabetes duration (years)	282	3.7 ± 4.6	384	3.3 ± 4.9	NS										

P values from *t* test.

with 63.7% in the surgical arm (χ^2 test $P < 0.001$). Remission in the surgical groups was 61%, 59%, and 92% in the SOS (1), the study by Dixon et al. (3), and the study by Mingrone et al. (5), respectively; the χ^2 test for the association between study and diabetes remission was significant ($P = 0.001$). This association is likely due to the association between diabetes remission and surgical technique ($P = 0.003$). All patients experienced remission in the BPD group (19 of 19 in the study by Mingrone et al.), 69% in the GBY group (47 of 68), 59% in the VBG group (116 of 198), and 63% in the GB group (55 of 87). The association between study and surgical technique was significant ($P < 0.001$).

Table 1 reports the comparisons between medical and surgical treatment at baseline and 2 years after enrollment in terms of both absolute values and percent changes. Patients in the medical arm presented at baseline with lower average weight, waist circumference, BMI, SBP, and DBP than surgical patients ($P < 0.001$ for all comparisons). Weight, waist circumference, BMI, glycemic control, lipid profile, and blood pressure were substantially improved after surgery. Supplementary Table 3 reports the P values from t tests related to the comparisons between medical therapy and each surgical procedure type.

Seventy-six percent of patients in the GD group and 60% in the GO group experienced diabetes remission ($P = 0.016$). Eighty-five percent of the patients in the GD group and 78% in the GO group achieved tight glycemic control (fasting glycemia <7 mmol/L) without pharmacological therapy; these figures increased to 91% and 88%, respectively, with pharmacological treatment. The number of patients with HbA_{1c} <7% (HbA_{1c} data available in a subset of 67 patients) without pharmacological therapy was similar (90% vs. 89%) in the two groups. There were no statistically significant differences between surgical groups. In the medical group, independently of pharmacological treatment, the percentage of patients with fasting glycemia <7 mmol/L was 38% and that with HbA_{1c} <7%, 38.6%.

ANOVA for Responders and Nonresponders

Table 2 reports baseline and end-of-study values of the putative predictive characteristics. To test whether baseline conditions were different between

Table 2—Baseline and 2-year values overall and by type of surgical procedure in patients who did or did not achieve diabetes remission

		Overall		GO		GD	
Variable	RESP	*n*	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD
Baseline							
Age (years)	0	135	48.7 ± 6.1	114	49.4 ± 5.8	21	45.4 ± 6.8
	1	234	47.7 ± 6.5	171	48.3 ± 6.0	63	46.1 ± 7.6
	Total	369	48.10 ± 6.4	285	48.7 ± 5.9	84	45.9 ± 7.3
Weight (kg)	0	135	118.77 ± 15.6	114	118.1 ± 15.4	21	122.2 ± 16.9
	1	237	124.15 ± 21.9	171	121.8 ± 20.6	66	130.2 ± 23.9
	Total	372	122.20 ± 20.0	285	120.3 ± 18.8	87	128.2 ± 22.6
Waist circumference (cm)	0	135	126.29 ± 11.0	114	126.1 ± 10.6	21	127.3 ± 13.6
	1	235	127.92 ± 14.0	169	127.5 ± 13.6	66	129.1 ± 15.1
	Total	370	127.33 ± 13.0	283	126.9 ± 12.4	87	128.6 ± 14.7
BMI (kg/m^2)	0	135	40.99 ± 4.0	114	40.7 ± 39	21	42.8 ± 4.3
	1	237	42.48 ± 5.3	171	41.8 ± 5.0	66	44.1 ± 5.7
	Total	372	41.94 ± 4.9	285	41.4 ± 4.6	87	43.8 ± 5.4
Glycemia (mmol/L)	0	134	9.71 ± 2.8	113	9.6 ± 2.6	21	10.4 ± 3.4
	1	237	8.10 ± 2.4	171	7.9 ± 2.1	66	8.6 ± 3.1
	Total	371	8.68 ± 2.7	284	8.6 ± 2.5	87	9.1 ± 3.2
Insulinemia (mU/L)	0	133	26.19 ± 15.0	112	26.8 ± 15.9	21	22.8 ± 9.2
	1	235	26.72 ± 13.1	170	28.4 ± 13.8	65	22.4 ± 10.0
	Total	368	26.53 ± 13.8	282	27.8 ± 14.7	86	22.5 ± 9.7
HbA_{1c} (%)	0	15	8.02 ± 0.8	12	7.9 ± 0.9	3	8.3 ± 0.6
	1	52	8.47 ± 1.6	17	7.7 ± 1.4	35	8.8 ± 1.6
	Total	67	8.37 ± 1.5	29	7.8 ± 1.2	38	8.8 ± 1.5
HOMA-IR (mmol/L · mU/L / 22.5)	0	132	11.41 ± 7.8	111	11.7 ± 8.3	21	10.1 ± 4.7
	1	235	9.56 ± 5.5	170	9.9 ± 5.7	65	8.5 ± 4.7
	Total	367	10.22 ± 6.5	281	10.6 ± 6.9	86	8.9 ± 4.7
SBP (mmHg)	0	123	152.63 ± 20.8	102	152.1 ± 19.9	21	155.3 ± 25.2
	1	219	149.78 ± 20.0	153	148.7 ± 18.6	66	152.4 ± 22.8
	Total	342	150.81 ± 20.3	255	150.0 ± 19.2	87	153.1 ± 23.2
DBP (mmHg)	0	123	91.71 ± 11.3	102	91.8 ± 10.4	21	91.2 ± 15.2
	1	219	92.27 ± 11.9	153	92.0 ± 11.2	66	92.8 ± 13.4
	Total	342	92.07 ± 11.6	255	91.9 ± 10.9	87	92.4 ± 13.7
HDL cholesterol (mmol/L)	0	128	1.24 ± 0.3	107	1.2 ± 0.3	21	1.3 ± 0.3
	1	220	1.22 ± 0.3	155	1.2 ± 0.3	65	1.2 ± 0.3
	Total	348	1.23 ± 0.3	262	1.2 ± 0.3	86	1.2 ± 0.3
Total cholesterol (mmol/L)	0	135	5.72 ± 1.2	114	5.8 ± 1.2	21	5.4 ± 1.1
	1	236	5.84 ± 1.3	170	6.0 ± 1.3	66	5.4 ± 1.3
	Total	371	5.80 ± 1.3	284	5.9 ± 1.2	87	5.4 ± 1.2
LDL cholesterol (mmol/L)	0	128	3.2 ± 1.0	107	3.2 ± 1.0	21	3.1 ± 1.0
	1	220	3.4 ± 1.0	155	3.5 ± 1.0	65	3.2 ± 1.2
	Total	348	3.3 ± 1.0	262	3.4 ± 1.0	86	3.2 ± 1.1
Triglycerides (mmol/L)	0	135	2.73 ± 1.4	114	2.8 ± 1.5	21	2.2 ± 0.8
	1	236	2.82 ± 2.5	170	3.0 ± 2.6	66	2.3 ± 1.9
	Total	371	2.79 ± 2.1	284	2.9 ± 2.2	87	2.2 ± 1.7
	0	122	6.21 ± 6.7	102	5.3 ± 5.7	20	10.8 ± 9.2
Diabetes duration (years)	1	220	1.78 ± 2.6	154	1.0 ± 1.9	66	3.6 ± 2.9
	Total	342	3.36 ± 4.9	256	2.7 ± 4.4	86	5.3 ± 5.9
2 years after surgery							
Weight (kg)	0	135	98.5 ± 17.2	114	99.8 ± 17.5	21	91.5 ± 13.3
	1	236	91.9 ± 17.5	170	93.6 ± 17.4	66	87.5 ± 17.1
	Total	371	94.3 ± 17.6	284	96.0 ± 17.7	87	88.5 ± 16.3
Waist circumference (cm)	0	134	110.2 ± 14.3	113	111.7 ± 14.3	21	102.0 ± 11.6
	1	236	104.6 ± 13.9	170	106.1 ± 13.0	66	100.8 ± 15.2
	Total	370	106.6 ± 14.3	283	108.3 ± 13.8	87	101.1 ± 14.4
BMI (kg/m^2)	0	135	34.0 ± 5.2	114	34.3 ± 5.2	21	32.2 ± 4.6
	1	236	31.4 ± 4.6	170	32.1 ± 4.5	66	29.7 ± 4.3
	Total	371	32.4 ± 5.0	284	33.0 ± 4.9	87	30.3 ± 4.5
Glycemia (mmol/L)	0	135	6.9 ± 2.6	114	6.8 ± 2.3	21	7.2 ± 3.8
	1	237	4.3 ± 0.6	171	4.4 ± 0.6	66	4.2 ± 0.7
	Total	372	5.2 ± 2.0	285	5.3 ± 1.9	87	4.9 ± 2.3

Continued on p. 170

Table 2—Continued

Variable	RESP	Overall *n*	Overall Mean ± SD	GO *n*	GO Mean ± SD	GD *n*	GD Mean ± SD
Insulinemia (mU/L)	0	135	15.2 ± 8.7	114	16.2 ± 8.9	21	10.0 ± 5.9
	1	237	10.8 ± 6.4	171	12.0 ± 6.7	66	7.8 ± 4.4
	Total	372	12.4 ± 7.7	285	13.7 ± 7.9	87	8.3 ± 4.9
HbA_{1c} (%)	0	15	6.7 ± 1.6	12	6.2 ± 0.8	3	8.6 ± 2.5
	1	52	5.5 ± 0.7	17	5.8 ± 0.5	35	5.4 ± 0.7
	Total	67	5.8 ± 1.0	29	5.9 ± 0.7	38	5.6 ± 1.3
HOMA-IR (mmol/L · mU/L / 22.5)	0	135	4.9 ± 4.3	114	5.2 ± 4.6	21	3.0 ± 1.6
	1	237	2.1 ± 1.3	171	2.4 ± 1.4	66	1.5 ± 1.0
	Total	372	3.1 ± 3.1	285	3.5 ± 3.4	87	1.9 ± 1.3
SBP (mmHg)	0	123	143.2 ± 23.1	102	143.3 ± 22.1	21	142.6 ± 28.0
	1	217	137.7 ± 20.6	151	140.2 ± 22.5	66	132.1 ± 13.7
	Total	340	139.7 ± 21.6	253	141.4 ± 22.4	87	134.6 ± 18.6
DBP (mmHg)	0	123	85.6 ± 11.6	102	86.4 ± 10.9	21	82.0 ± 14.2
	1	217	84.2 ± 10.6	151	85.1 ± 11.5	66	82.2 ± 7.8
	Total	340	84.7 ± 11.0	253	85.6 ± 11.3	87	82.1 ± 9.7
HDL cholesterol (mmol/L)	0	133	1.4 ± 0.3	112	1.4 ± 0.3	21	1.5 ± 0.3
	1	230	1.5 ± 0.4	165	1.5 ± 0.37	65	1.5 ± 0.4
	Total	363	1.5 ± 0.4	277	1.5 ± 0.35	86	1.5 ± 0.4
Total cholesterol (mmol/L)	0	135	5.5 ± 1.2	114	5.7 ± 1.16	21	4.8 ± 1.0
	1	236	5.4 ± 1.4	171	5.8 ± 1.12	65	4.2 ± 1.4
	Total	371	5.4 ± 1.3	285	5.7 ± 1.14	86	4.4 ± 1.3
Triglycerides (mmol/L)	0	135	2.0 ± 1.1	114	2.1 ± 1.17	21	1.4 ± 0.4
	1	236	1.5 ± 0.8	171	1.7 ± 0.88	65	1.1 ± 0.5
	Total	371	1.7 ± 1.0	285	1.8 ± 1.03	86	1.2 ± 0.5
LDL cholesterol (mmol/L)	0	133	3.2 ± 1.0	112	3.3 ± 1.0	21	2.6 ± 1.0
	1	230	3.2 ± 1.1	165	3.5 ± 1.0	65	2.2 ± 1.1
	Total	363	3.2 ± 1.1	277	3.4 ± 1.0	86	2.3 ± 1.0

RESP, responder (0 = nonresponder; 1 = responder).

surgical techniques and whether responders and nonresponders were different at baseline, an ANOVA with two between-factor components (remission and surgical procedure) was performed for each baseline variable (Supplementary Table 4). Patients allocated to the diversionary (GD) procedures were younger and more obese and presented with a more compromised glycemic control, including a significantly lower baseline insulinemia; higher, though not statistically significant, glycemia; higher HbA_{1c}, and longer diabetes history. The lower HOMA-IR score in the GD group (8.9 ± 4.7 vs. 10.6 ± 6.9) might be ascribed to lower fasting plasma insulin levels. Baseline cholesterol and triglyceride levels were also lower in the GD group.

All interaction terms except diabetes duration (P = 0.015) were nonsignificant. Nonresponders in the GD group had a longer history of diabetes than those in the GO group.

The Supplementary Data report the mean values and SDs of the variables by surgical procedure at baseline (Supplementary Table 5) and 2 years after surgery (Supplementary Table 6) and the percent changes (Supplementary Table 1). Greater effects on weight loss, fat distribution, glycemia, HbA_{1c}, and HOMA-IR were observed after RYGB and BPD; in contrast, the type of bariatric surgery did not affect blood pressure outcomes. Supplementary Table 7 reports the P values related to ANOVA with variables at baseline and with between-factor remission and surgical techniques at four levels. Responders had lower glycemia, HOMA-IR, and diabetes duration than nonresponders.

Predictors of Diabetes Remission

Results of the logistic multivariable models are reported in Table 3. Separate analyses were conducted overall, for the medical group, for the surgical group, and separately for the GO and GD groups. In the total population at baseline, younger age, shorter diabetes duration, lower fasting glycemia, and no antidiabetic drugs predicted a higher probability of diabetes remission at 2 years. However, age did not remain a significant predictor in the subgroup analyses. In the surgical group, BMI was a significant predictor but lost significance when type of surgery was taken into account. When GO was considered, diabetes duration, fasting glycemia, and therapy for diabetes were inversely correlated with diabetes remission; in GD, only fasting glycemia was a significant predictor.

To better understand the role of BMI in determining remission, a categorical variable stratifying patients into three degrees of obesity was calculated. The considered BMI classes were BMI ≤35, 35<BMI≤40, and BMI >40 kg/m^2. Odds ratios were calculated considering BMI ≤35 kg/m^2 as the reference. Estimated risk for diabetes remission was 2.9 (95% CI 1.43–5.80) for patients with BMI >40 kg/m^2 (P = 0.003). No significant difference was founded between classes BMI ≤35 and 35<BMI≤40 kg/m^2.

Criteria for Predicting Remission

Table 3 also reports results from the ROC analyses. An independent ROC analysis was performed for baseline fasting glycemia, diabetes duration, and BMI to provide the best cutoff values for the prediction of remission independently of the surgical procedure performed. These cutoffs were BMI ≥44 kg/m^2, baseline glycemia ≤7.65 mmol/L, and diabetes duration ≤1.5 years.

Table 3—Prediction of diabetes remission: logistic models and ROC analyses

	Overall		Medical*		Surgical overall C (n = 415)				GO		GD	
	A (n = 727)		B (n = 312)		Without T. of S. C1		With T. of S.** C2		D (n = 318)		E (n = 97)	
Variable	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value	β	*P* value
Logistic regression after stepwise elimination												
Intercept	3.71	<0.001	1.895	0.103	0.089	0.942	2.83	<0.001	3.27	<0.001	2.838	<0.001
Age	−0.042	0.005										
Fasting glycemia (mmol/L)	−0.118	0.004	−0.306	0.051	−0.145	0.004	−0.141	0.011	−0.186	0.006		
Diabetes duration	−0.192	<0.001	−0.910	0.013	−0.210	<0.001	−0.220	<0.001	−0.197	0.004	−0.273	<0.001
BMI					0.059	0.036						
T. of S.							2.180	<0.001				
Type of therapy (level 1)	−0.819	<0.001	−2.247	0.042			−1.22	<0.001	−1.364	<0.001		
Type of therapy (level 2)	−0.282	0.473	0.832	0.582			−1.13	0.054	−1.783	0.03		

	Univariate ROC analysis					
	F		G		H	
	Cutoff (Sens., Spec.)	AUC (95% CI)	Cutoff (Sens., Spec.)	AUC (95% CI)	Cutoff (Sens., Spec.)	AUC (95% CI)
ROC analysis						
BMI	≥44 (32%, 83%)	0.58 (0.52–0.64)				
Fasting glycemia (mmol/L)	≤7.65 (59.1%, 73.1%)	0.69 (0.63–0.75)	≤7.6 (62.6%, 72.6%)	0.71 (0.65–0.77)		
Diabetes duration	≤1.5 (65.9%, 73.8%)	0.74 (0.68–0.79)	≤1.5 (77.9%, 70.6%)	0.78 (0.72–0.84)	≤7.5 (92.4%, 55%)	0.75 (0.61–0.90)

Sens., sensitivity; Spec., specificity; T. of S., type of surgery (GO vs. GD). *A further model including percent weight change was tested; results were β = −0.41 (*P* = 0.009) for basal glycemia, β = −0.53 (*P* < 0.001) for diabetes duration, and β = −0.09 (*P* = 0.005). **When type of surgery was included in the model, BMI was no longer significant.

Additionally, two multivariate ROC analyses were performed on the probabilities determined from the two logistic models fitted to the surgical group. The first logistic model included baseline BMI, glycemia, and diabetes duration, and the second included baseline glycemia, diabetes duration, type of surgery, and type of therapy. Figure 1*A* and *B* show the ROC curves of these multivariate ROC analyses. Columns G and H in Table 3 report an independent ROC analysis separately for type of surgery, showing cutoffs for those variables identified as significantly associated in the multivariate logistic regressions.

Improvement of Glucose Control With Respect to Baseline Conditions

The only baseline factors that significantly correlated with percent change in glycemia were glycemia, HbA_{1c}, and HOMA-IR ($P < 0.001$). However, the percent change in HbA_{1c}, available from the studies by Dixon et al. (3) and Mingrone et al. (5), was significantly negatively correlated with the following baseline factors: glycemia ($P = 0.001$), HbA_{1c} ($P = 0.001$), weight ($P = 0.001$), waist circumference ($P < 0.001$), BMI ($P = 0.01$), total cholesterol ($P = 0.02$), and triglycerides ($P < 0.001$).

In a multivariate linear model with percent change in HbA_{1c} as the dependent variable, the significant predictors included in the final model, after a stepwise elimination, were baseline waist circumference, glycemia, and triglycerides (regression coefficient $\beta = -0.31$ [$P = 0.008$], -1.46 [$P = 0.02$], and -3.79 [$P = 0.02$], respectively). When only the GO surgical technique was considered, results were quite similar. In the GD group, percent change in HbA_{1c} correlated negatively with baseline waist circumference ($P = 0.014$), total cholesterol ($P = 0.013$), and triglycerides ($P = 0.006$), whereas final HbA_{1c} correlated only with total cholesterol ($P = 0.044$).

Diabetes Remission, Surgical Techniques, and Glucose Control Changes

For the change in each variable (glycemia, HbA_{1c}, etc.), an ANOVA (Supplementary Table 4) with between-factor comparisons of remission and type of surgical technique was performed to test for differences between responders

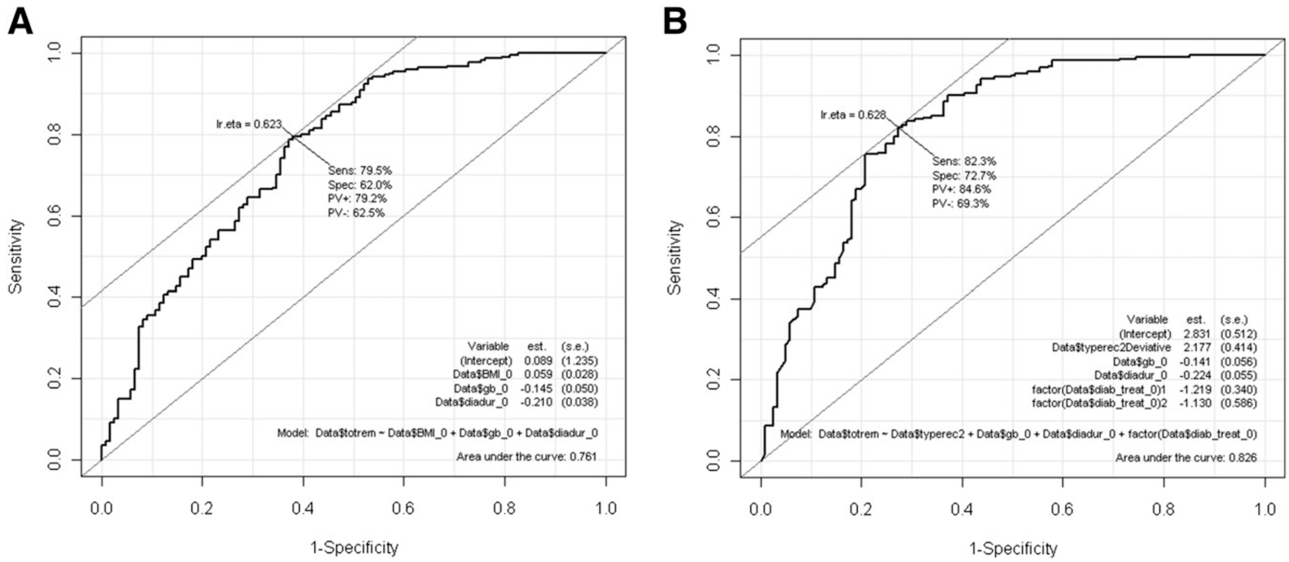

Figure 1—Multivariate ROC curves from logistic regression in the overall sample of surgical patients with (*A*) or without (*B*) type of surgery as predictor. Values related to lr.η refer to the best cutoff for probability of remission. diab_treat, diabetes treatment; diadur, diabetes duration; gb, glycemia at baseline; PV−, negative predictive value; PV+, positive predictive value; Sens, sensitivity; Spec, specificity; totrem, total remission; typerec, type of surgery.

and nonresponders and between GO and GD procedures. All interaction terms except for HbA_{1c} were not significant.

Weight Loss and Waist Circumference

Percent changes in weight were −17.1 ± 9.1% and −25.5 ± 10.4% in nonresponders and responders and −20.0 ± 10.0% and −30.5 ± 9.1% in the GO and GD groups ($P < 0.001$), and percent changes in waist circumference were −12.7 ± 8.5% and −18.0 ± 8.9% in nonresponders and responders and −14.4 ± 8.8% and −21.3 ± 8.2% in the GO and GD groups ($P < 0.001$), respectively. Diabetes remission is explained by percent weight loss after controlling for baseline variables. After applying a multivariable logistic regression model with a stepwise elimination criterion, the final model included percent change in weight, fasting glycemia, and diabetes duration, with $P < 0.001$ for all variables.

Glycemic Control Improvement

As shown by ANOVA, two factors (responders and type of operation) significantly affected the changes in glycemia, insulinemia, HbA_{1c}, and HOMA-IR. Change in glycemia was smaller in nonresponders than in responders (−25.1 ± 29.4% vs. −42.9 ± 15.5%) and with GO versus GD technique (−34.8 ± 22.6% vs. −41.9 ± 24.1%). Similar results were obtained for variation in HbA_{1c} (−16.5 ± 20.3% vs. −32.8 ± 13.9% in nonresponders vs. responders and −22.6 ± 11.9% vs. −34.1 ± 18.4% for GO vs. GD, respectively). The interaction was highly significant ($P < 0.001$), although in the GO group, nonresponders and responders experienced similar variations (−22.04 ± 9.75% vs. −23.05 ± 13.54%, respectively), and in the GD group, nonresponders experienced increased and responders experienced strongly decreased HbA_{1c} values (5.64 ± 37.9% vs. −37.50 ± 11.54%, respectively). Consequently, HOMA-IR followed the same trend (−49.3 ± 38.3% vs. −73.7 ± 17.9% in nonresponders and responders and −61.4 ± 31.8% vs. −76.5 ± 15.4% for GO vs. GD, respectively).

Lipid Profile Improvement

Changes in lipid profile are summarized in Fig. 2. Total cholesterol, LDL cholesterol, and triglycerides decreased more after the GD than after the GO procedure; in addition, triglycerides decreased more in responders than in nonresponders. Table 2 reports the mean values at baseline and at 2 years by remission and type of surgical technique.

Glycemic Control Improvements and Weight Loss

The influence of weight loss, waist circumference reduction, and type of surgery on remission was also studied by means of logistic regression. The only significant factor associated with remission was percent change in weight ($P < 0.001$), which explained 12% of the variance; the same results were obtained when change in HbA_{1c} was related with percent change in weight, percent change in waist circumference, and type of surgery in a multivariate linear model.

From the ROC analysis, a cutoff value of percent weight change was identified (−24%) with a specificity of 80% and a sensitivity of 55%. AUC was 73.1% (95% CI 67.8–78.3%). Weight change was −19.99 ± 10.01% in the GO group and −30.52 ± 9.08% in the GD group. When the four procedures were considered separately, the percentage of subjects who experienced a weight change greater than the calculated cutoff was 24% for GB, 33% for VBG, 75% for RYGB, and 79% for BPD.

Association Between Study Center and Diabetes Remission

A Fisher exact test for the association between study center and diabetes remission was significant ($P < 0.001$) likely because of the association between diabetes remission and the surgical technique ($P = 0.007$) used in the different studies.

CONCLUSIONS

This study, based on a sample of 727 patients of whom 415 underwent bariatric surgery, is the first large analysis to focus on the best predictors of diabetes

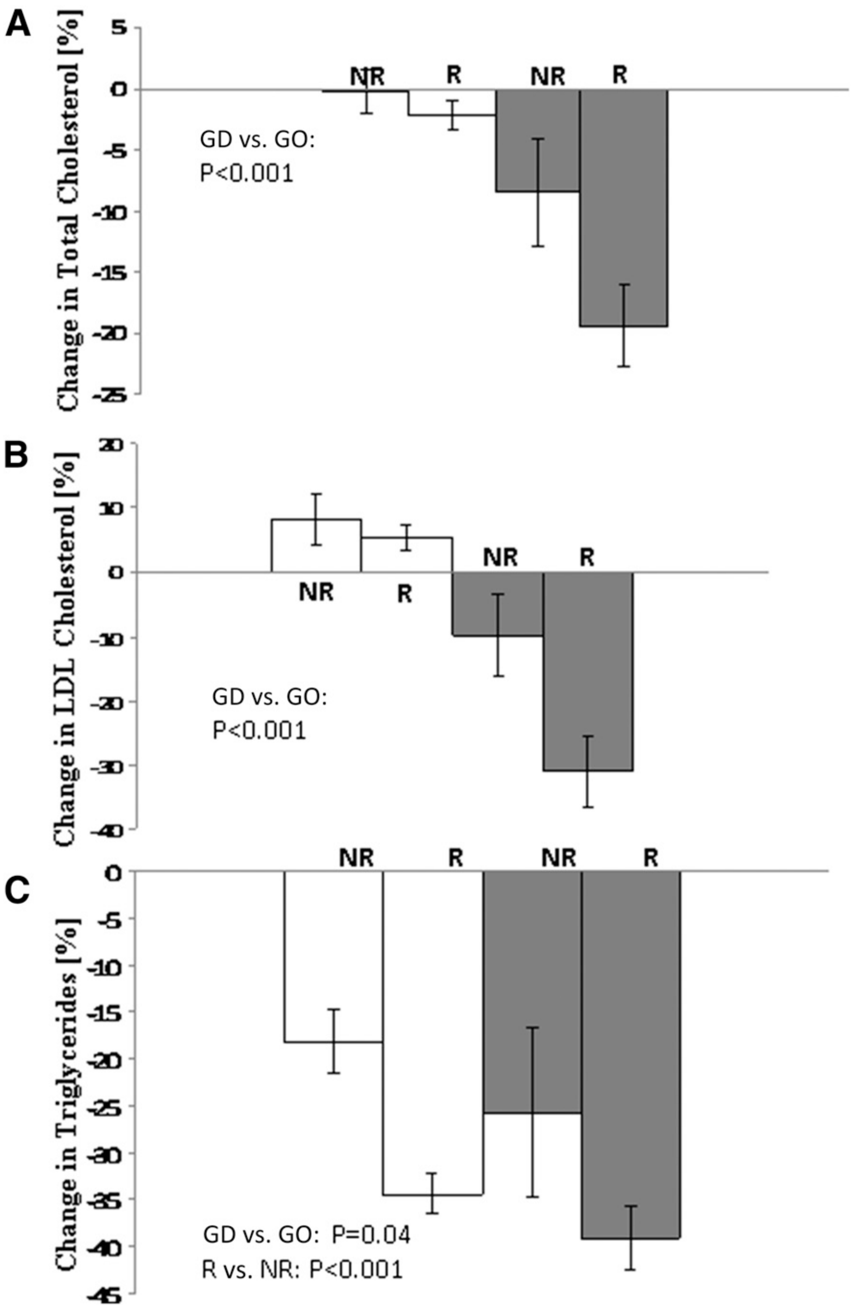

Figure 2—Percent changes at 2 years with respect to baseline values of total cholesterol (*A*), LDL cholesterol (*B*), and triglycerides (*C*) in nonresponders and responders in the GO (open bars) and GD (solid bars) groups. Significant *P* values of the two factors (diabetes remission: responders vs. nonresponders; surgical procedure: GO vs. GD) are shown. NR, nonresponders; R, responders.

remission after bariatric surgery in a Caucasian population and to highlight the differences between so-called responders and nonresponders. As a result, we have reinforced that bariatric surgery restores euglycemia in a significant number of subjects with diabetes, at least in the short term. The major findings of the study are as follows:

1. Diabetes remission, defined as fasting glycemia <5.6 mmol/L without pharmacological therapy, occurred in 63.7% of the patients in the surgical arm and 14.4% of those in the medical arm.
2. Ninety percent of surgically treated patients and $<40\%$ of medically treated patients achieved tight glycemic control at 2 years.
3. GD procedures were more effective than GO procedures in terms of diabetes remission (76% vs. 60%), the former being associated with a higher diabetes remission rate (not correlated with the use of insulin before surgery), even though diabetes duration was much longer (7.5 vs. 1.5 years).
4. The "risk" of remission was not statistically significant between subjects with BMI ≤ 35 and $35 < \text{BMI} \leq 40$ kg/m^2.

In the surgical population as a whole and in agreement with the literature (9–12), the longer the diabetes duration before bariatric surgery and the lower usage of antidiabetic drugs, particularly insulin, the lower the diabetes remission rate. The metric duration of the clinical diagnosis of diabetes together with the type of medication used can be considered a surrogate measure of the preservation of islet secretory capacity, suggesting that the more severe the diabetes, the lower the remission rate. However, we emphasize that although duration of diabetes ≤ 1.5 years, fasting glycemia ≤ 7.6 mmol/L, and absence of insulin therapy predicted a better outcome after purely restrictive operations, these parameters did not influence the effect of RYGB and BPD on diabetes remission, which also occurred when diabetes duration was much longer (up to 7.5 years) and patients were receiving insulin treatment and had worse glycemic control.

Overall, the best predictors of improvement in glycemic control after bariatric surgery were smaller waist circumference, better-controlled diabetes, and lower triglyceride levels at baseline. In addition, responders lost more weight and waist circumference after bariatric surgery, had a greater reduction in plasma triglycerides, and became more insulin sensitive.

Abdominal obesity (measured by the waist circumference) is a more powerful predictor of T2D and cardiovascular disease development than obesity itself (measured by BMI) (13–16). In another study, a waist circumference ≥ 94 cm in middle-aged men identified subjects at risk for T2D and cardiovascular disease, with a sensitivity of 84.4% (17). These data together with the finding that the remission rate was not statistically different in subjects with BMI 30–35 versus 35–40 kg/m^2 suggest that abdominal obesity metrics might be a better anthropometric measure than BMI as an indicator of eligibility for bariatric surgery.

A limitation of the present study is that in the merged database, HbA_{1c} values were available only for the studies by Dixon et al. (3) and Mingrone et al. (5), whereas the largest number of subjects were acquired from the SOS database (1), which started when the measurement of glycated hemoglobin was not routinely performed to monitor glycemic control. Dixon et al. (18) more recently demonstrated that Chinese patients with T2D from Taiwan show a glycemic response to RYGB related to baseline BMI, duration of diabetes, circulating fasting C-peptide levels, and the degree of weight loss. These results in this relatively small Asian sample (154 subjects) are not fully confirmed in the present investigation in a much larger sample of Caucasian subjects and of various types of bariatric surgery. These differences may depend on ethnicity; however, differences in the criteria used to define remission cannot be discounted as a reason. Of note, in the Asian sample, patients with preoperative BMI as low as 23 kg/m^2 were included, and BMI <27 kg/m^2 predicted poor glycemic control (18,19), possibly indicating that BMI is only a clinically important predictive factor when considering patients in the nonobese range.

The present study based on baseline and 2-year postoperative data was unable to discriminate between early and late effects of bariatric surgery; thus, we cannot infer the different mechanisms of action of GO versus GD operations. We found that weight loss represents a major determinant of end-study glycemic control. GD procedures were much more effective than GO procedures in achieving diabetes remission, although it is not clear whether this is purely because of the superior weight loss achieved with the GD procedures.

The current results regarding longer diabetes duration and prediction of diabetes remission (which is still possible after GD procedures for disease duration as long as 7.5 years) do not imply that it is useful to wait a long time before undergoing bariatric surgery. The SOS study, in fact, recently demonstrated that the shorter the diabetes duration, the lower the incidence of diabetes complications (20).

In conclusion, the predictors of diabetes remission vary in relation to the type of bariatric surgery, whereas better glycemic control after surgery is achieved in individuals with smaller waist circumference at baseline. Furthermore, the effect of bariatric surgery on diabetes remission seems to be independent of baseline BMI, suggesting that bariatric surgery could be a therapeutic option for patients with T2D and abdominal obesity, even with BMI between 30 and 35 kg/m^2.

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Author Contributions. S.P. contributed to the study concept and design, data analysis and interpretation, and drafting of the manuscript. L.C. contributed to the study concept and design and critical revision of the manuscript for important intellectual content. A.D.G. contributed to the data analysis. M.P. contributed to the statistical analysis and critical revision of the manuscript for important intellectual content. T.R. and L.S. contributed to the critical revision of the manuscript for important intellectual content. G.M. contributed to the study concept and design, data interpretation, and drafting of the manuscript. J.B.D. contributed to the study concept and design, data interpretation, and critical revision of the manuscript for important intellectual content. S.P. and G.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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