Weight Change–Adjusted Effects of Gastric Bypass Surgery on Glucose Metabolism: 2- and 10-Year Results From the Swedish Obese Subjects (SOS) Study

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OBJECTIVE

It has been suggested that weight change–independent effects on fasting insulin and glucose levels are present after gastric bypass (GBP) but not after banding and vertical banded gastroplasty (VBG). We therefore evaluated weight change–adjusted effects of GBP, compared with restrictive surgical procedures, on long-term changes in fasting levels of glucose, insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) in the Swedish Obese Subjects (SOS) study.

RESEARCH DESIGN AND METHODS

Participants who completed the 2-year (n = 1,762) and/or the 10-year (n = 1,216) follow-up were divided into three weight change classes (weight loss >30%, 20–30%, or ≤20%), and by surgical method (banding, VBG, or GBP). Glucose, insulin, and HOMA-IR changes were analyzed in relation to weight change over 2 and 10 years. Analyses were performed in the full cohort and also in subgroups based on baseline glucose status.

RESULTS

Within weight change classes, reductions in glucose, insulin, and HOMA-IR were similar in the three surgery groups both at 2 and at 10 years. Reductions in glucose, insulin, and HOMA-IR increased with increasing weight loss, and changes were typically related to weight change within each surgery group. Moreover, the association between weight change and change in glucose, insulin, or HOMA-IR did not differ between the surgery groups at 2 and 10 years. When patients were subdivided also by baseline glucose status, similar relationships between weight changes and changes in glucose, insulin, and HOMA-IR were observed.

CONCLUSIONS

Even though weight loss–independent effects are important for short-term diabetes remission, our results suggest that degree of weight loss is more important for long-term reductions in fasting insulin and glucose than choice of bariatric surgery procedure.

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CARDIOVASCULAR AND METABOLIC RISK

Type 2 diabetes is related to obesity and characterized by elevated fasting plasma glucose concentrations (1,2) due to insulin resistance, with high hepatic glucose output and decreased glucose uptake in peripheral tissues (3). Type 2 diabetes is a chronic condition, but over the last 15 years it has been shown repeatedly (4–14) that bariatric surgery is associated with a high diabetes remission rate, and a systematic review concluded that 78% of patients with diabetes achieved resolution in the first 2 years after surgery (rev. in 6). Long-term results (10–15 years) also demonstrate high remission rates as well as reduced incidence of diabetes complications in surgery patients (15,16).

Gastric bypass (GBP) is associated with more pronounced effects on glucose homeostasis short term compared with gastric banding and other restrictive procedures (6). It has been suggested that early remission of diabetes after GBP is caused by surgery-specific, weight loss–independent effects on glucose homeostasis (17,18). Changes in the postprandial secretory pattern of incretins, such as glucagon-like peptide 1, are generally suggested as the major component of this effect, although alterations in dietary habits, gastric emptying, bile acids, and/or microbiota have also been put forward as possible mechanisms that could explain this phenomenon (19). Indeed, remission of type 2 diabetes has been reported within days to weeks after GBP surgery, before substantial weight reduction has occurred (20,21).

The changes in the incretin secretion patterns occur in the first few months after surgery, but weight loss change persists over a long time. In most studies, results suggest that GBP is more effective for achieving major weight reduction and higher rates of diabetes remission compared with restrictive procedures (5,8,10). However, adjustments for degree of weight loss have seldom been performed in these analyses, and some reports indicate that magnitude of weight loss is the major determinant of whether obese patients with diabetes achieve remission both up to and after 2 years (6,12,22–24). Furthermore, several recent studies challenge the importance of the incretin effect, implying that caloric restriction could instead be a main explanatory factor (25–29).

As part of the Swedish Obese Subjects (SOS) study, we have previously published several reports on the long-term (10–20 years) effects of bariatric surgery (4,15,30–34). Similar to the reports referenced above, our data suggest that weight loss and risk factor changes are most prominent for patients treated with GBP (4). However, whether weight loss–independent effects on fasting insulin and glucose levels are present after GBP but not after banding and VBG procedures has not been analyzed. Therefore, in the current report we evaluate weight loss–independent effects of GBP compared with restrictive surgical procedures on changes in fasting glucose and insulin levels over 2 and 10 years of follow-up.

RESEARCH DESIGN AND METHODS

General Study Design

The nonrandomized prospective SOS intervention trial enrolled 4,047 obese subjects (34,35). In brief, 6,905 subjects participated in an initial matching examination. In this examination, 5,335 individuals were found to be eligible. (See below.) Among eligible patients, 2,010 choosing surgery formed the surgery group and a contemporaneously matched control group (n = 2,037) was created using 18 matching variables. The two study groups had identical inclusion and exclusion criteria. The inclusion criteria were age 37–60 years and BMI ≥34 kg/m^2 for men and ≥38 kg/m^2 for women before or at the matching examination. The exclusion criteria were few and were aimed at obtaining operable subjects. Baseline examinations of subjects in both groups took place 4 weeks before surgery. The intervention began on the day of surgery for subjects in the surgery group and for their matched control subjects. Patients were then re-examined after 0.5, 1, 2, 3, 4, 6, 8, 10, 15, and 20 years (34). Seven regional ethics review boards approved the study protocol, and informed consent was obtained from all subjects. Of the 2,010 subjects in the surgery group, 376 underwent nonadjustable or adjustable gastric banding, 1,369 underwent vertical banded gastroplasty (VBG), and 265 underwent GBP.

Report Population, Examinations, and Data Analysis

For the current report, only surgery patients were included. We used biochemical examinations, body weights, and other anthropometric measurements at baseline, 2 years, and 10 years. Fasting blood samples were obtained in the morning after an overnight fast. Fasting glucose concentrations were measured in venous whole blood from 1987 to 2009. After 2009, venous plasma glucose was measured and converted to blood glucose (conversion factor 1.12, R^2 = 98.9). Biochemical measurements were undertaken at the Central Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden. The laboratory is accredited according to International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) 15189:2007 standards.

Type 2 diabetes was defined as fasting blood glucose ≥6.1 mmol/L (corresponding to fasting plasma glucose ≥7.0 mmol/L) and/or self-reported therapy with glucose-lowering medications at baseline. Impaired fasting glucose was defined as fasting blood glucose ≥5.0 to <6.1 mmol/L (fasting plasma glucose ≥5.6 to <7.0 mmol/L) (2). The study was initiated before repeated measurements were routinely used for the diagnosis of type 2 diabetes; therefore, single fasting glucose determinations were used. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as fasting plasma insulin (pmol/L) × fasting plasma glucose (mmol/L)/135.

We analyzed glucose and insulin changes over 2 and 10 years in relation to weight change.

Patients who had been converted from the original to another surgical method between baseline and 2 years or baseline and 10 years were not included in the calculations (n = 67 and n = 307 patients were excluded from 2- and 10-year analyses, respectively).

Patients with missing values for body weight, glucose, and insulin at baseline or at the follow-up time points were excluded (a total of 29 and 30 patients for 2- and 10-year analyses, respectively). For the main analysis, patients were divided into three relative weight change classes (designated by percent weight change over 2 or 10 years: weight loss >30%, between 20 and 30%, or ≤20%) and by surgical method (banding, VBG, or GBP). For the subgroup analysis, patients were also subdivided by baseline glucose status; one group consisted of patients with normal fasting glucose at baseline, and one group consisted of patients with impaired fasting glucose or type 2 diabetes at baseline. The patients with impaired

Table 1—Baseline characteristics and weight changes in obese SOS surgery patients by 2- and 10-year weight change and type of surgery

	>30% weight change			20–30% weight change			≤20% weight change		
	Banding	VBG	GBP	Banding	VBG	GBP	Banding	VBG	GBP
2-year data									
Completers, *N* (%)*	71 (21)	258 (22)	140 (59)	90 (27)	419 (35)	68 (29)	170 (51)	516 (43)	30 (13)
Baseline data									
Males, %	27	31	21	27	26	28	36	31	40
Age, years	47 ± 6	47 ± 6	46 ± 6	48 ± 6	47 ± 6	48 ± 6	48 ± 6	48 ± 6	48 ± 6
BMI, kg/m^2	43.0 ± 4.2	43.7 ± 4.7	44.7 ± 5.4	41.6 ± 4.0	42.3 ± 3.9	42.7 ± 4.1	40.9 ± 4.3	41.4 ± 4.1	41.7 ± 4.0
Glucose, mmol/L	4.9 ± 1.5	5.0 ± 1.7	5.2 ± 1.8	4.7 ± 1.2	4.9 ± 1.9	5.8 ± 2.6	5.3 ± 2.0	5.3 ± 2.1	5.6 ± 2.7
Insulin, pmol/L	129 ± 79	127 ± 67	127 ± 69	116 ± 62	128 ± 72	116 ± 49	131 ± 69	130 ± 91	119 ± 56
HOMA-IR	5.0 ± 3.8	4.9 ± 3.5	5.0 ± 3.6	4.2 ± 2.8	4.9 ± 4.4	5.2 ± 3.6	5.6 ± 5.0	5.4 ± 5.1	4.9 ± 3.0
2-year changes									
Body weight change, kg	−46.9 ± 11.2	−44.7 ± 9.2	−48.2 ± 12.8	−29.7 ± 5.5	−29.4 ± 5.0	−31.4 ± 5.2	−14.6 ± 7.0	−16.2 ± 6.2	−19.3 ± 5.0
Body weight change, %	−38.0 ± 6.2	−35.8 ± 4.9	−37.7 ± 5.7	−24.9 ± 3.0	−24.7 ± 2.9	−25.8 ± 3.0	−12.1 ± 5.5	−13.7 ± 5.0	−16.2 ± 3.2
10-year data									
Completers, *N* (%)*	28 (14)	65 (8)	42 (25)	32 (16)	197 (23)	68 (40)	144 (71)	579 (69)	61 (36)
Baseline data									
Males, %	25	26	14	19	31	22	38	29	43
Age, years	47 ± 6	47 ± 6	47 ± 6	46 ± 6	47 ± 6	47 ± 6	48 ± 6	48 ± 6	48 ± 6
BMI, kg/m^2	44.0 ± 4.8	42.9 ± 4.2	43.8 ± 5.7	42.3 ± 3.3	42.3 ± 3.9	43.5 ± 4.4	40.6 ± 3.9	41.8 ± 4.1	41.9 ± 4.0
Glucose, mmol/L	5.2 ± 1.6	5.1 ± 2.0	4.9 ± 1.7	5.2 ± 1.7	5.3 ± 2.2	5.5 ± 2.2	4.9 ± 1.4	5.1 ± 2.0	5.4 ± 2.4
Insulin, pmol/L	133 ± 68	142 ± 187	108 ± 52	142 ± 75	128 ± 70	132 ± 65	121 ± 65	123 ± 64	115 ± 48
HOMA-IR	5.5 ± 4.1	5.8 ± 11.0	4.3 ± 3.8	5.6 ± 3.5	5.3 ± 4.8	5.6 ± 4.4	4.7 ± 3.7	4.8 ± 3.7	4.6 ± 2.6
10-year changes									
Body weight change, kg	−50.4 ± 10.8	−43.8 ± 8.0	−46.1 ± 13.1	−29.4 ± 4.6	−29.5 ± 5.1	−30.1 ± 4.5	−7.8 ± 9.9	−12.0 ± 8.4	−16.2 ± 7.4
Body weight change, %	−39.7 ± 5.9	−36.0 ± 4.5	−37.6 ± 5.6	−24.4 ± 3.0	−24.3 ± 2.8	−24.5 ± 2.6	−6.6 ± 8.4	−10.1 ± 6.9	−13.1 ± 5.4

Data are presented as mean ± SD. *Proportion within each surgery group achieving the different degree of weight change.

fasting glucose and patients with type 2 diabetes were pooled to obtain subgroups large enough to allow subgrouping by weight change class and surgery method.

Statistical Methods

Mean values, with SDs, and percentages were used to describe the baseline characteristics and changes over 2 and 10 years in different surgery groups. Changes in fasting glucose, insulin, and HOMA-IR were analyzed by ANCOVA in the three surgery groups, adjusting for baseline levels of respective variable, degree of weight change, sex, and age. Statistical analyses were performed with Stata software (version 12.1; College Station, TX). All P values are two sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics and 2-Year and 10-Year Weight Changes

Table 1 shows baseline characteristics and weight change by weight change class and type of surgery for all patients who completed the 2- and 10-year follow-up, respectively. Within given weight change classes, baseline glucose, insulin, and HOMA-IR did not differ between the three surgery groups. Supplementary Table 1 shows the baseline data and 2-year and 10-year weight changes separately for patients with normal fasting glucose and with impaired fasting glucose/type 2 diabetes. At the 2-year follow-up, ~20% of the banding and VBG patients achieved >30% weight loss compared with 59% in the GBP group. After 10 years, the percentages achieving >30% weight loss were 25% in the GBP group compared with 14% and 8% in the banding and VBG groups, respectively. The fractions of patients who completed the 2- and 10-year follow-up were 88% and 60%, respectively.

Changes in Glucose, Insulin, and HOMA-IR Over 2 and 10 Years

Within given weight change classes, fasting levels of glucose (Fig. 1*A*), fasting levels of insulin (Fig. 1*B*), and HOMA-IR (Fig. 1*C*) changes were similar after GBP, banding, and VBG both at 2 and at 10 years. In principle, the same was true within the normal fasting glucose and impaired fasting glucose/type 2 diabetes groups, although all changes were larger in the latter subgroup (Supplementary Figs. 1–3).

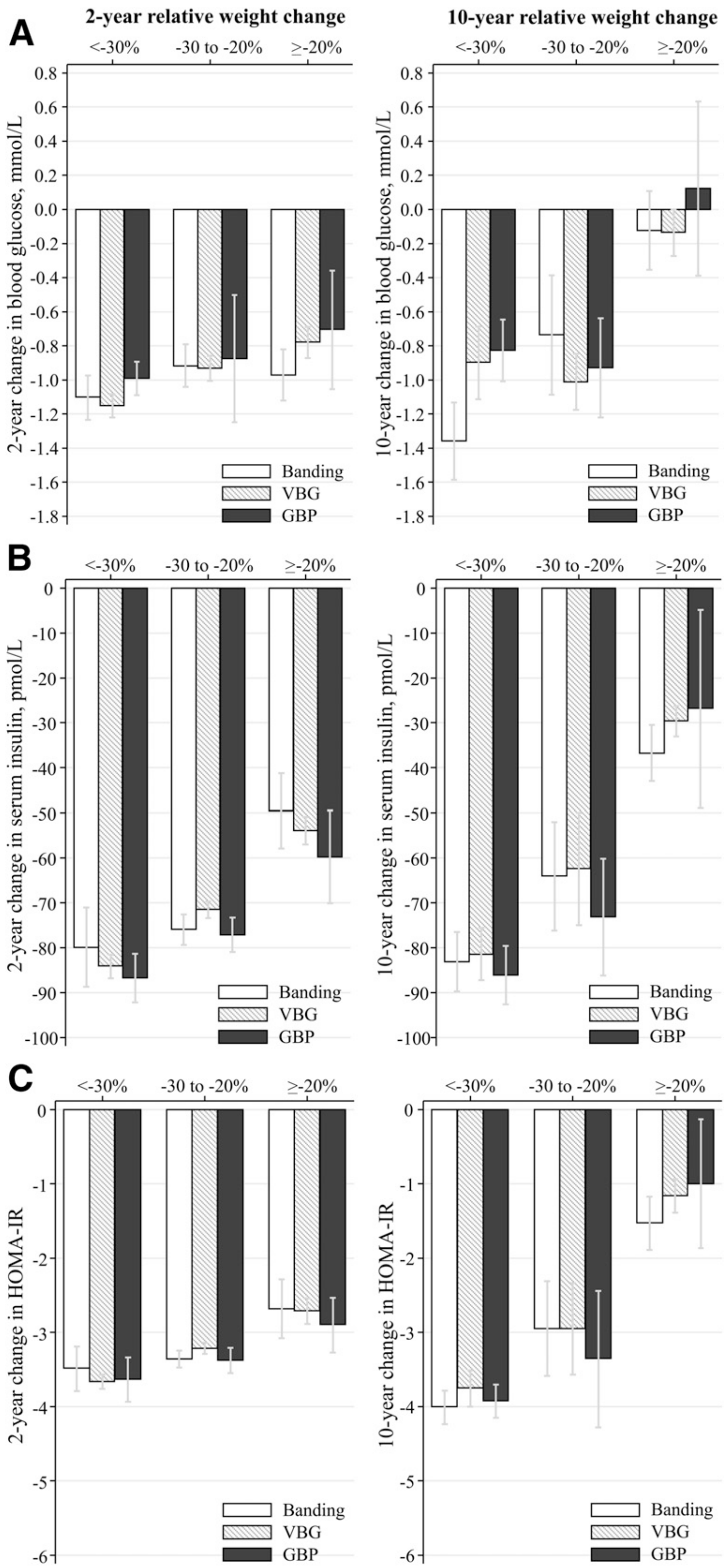

Figure 1—Two-year and 10-year changes in fasting blood glucose (*A*), fasting serum insulin (*B*), and HOMA-IR (*C*) by relative weight change class and type of bariatric surgery in all patients. Left panels: 2-year changes. Right panels: 10-year changes.

Figure 1*A*–*C* suggests that reductions in glucose, insulin, and HOMA-IR increase with increasing weight loss. Moreover, the slopes of the regression analyses revealed that weight changes at 2 and 10 years were, for all performed analyses, associated with changes in glucose, insulin, and HOMA-IR within each of the surgery groups (Table 2). Furthermore, when we specifically tested whether the association between weight change (%) and change in glucose, insulin, and HOMA-IR differed between the three surgery groups, we found that this was not the case. The regression slope for GBP was similar to the banding and VBG regression slopes both at 2 and at 10 years (Table 2) (P values for test of equal slopes all nonsignificant).

We also performed a regression analysis in the normal fasting glucose and impaired fasting glucose/type 2 diabetes subgroups. In Supplementary Table 2, slopes are shown separately for patients with normal fasting glucose and those with impaired fasting glucose/type 2 diabetes. For glucose, we were unable to detect a difference between GBP versus banding and VBG slopes in either group both at the 2-year and at the 10-year follow-up (Supplementary Table 2) (P values for test of equal slopes all nonsignificant). The above was true also for insulin and HOMA-IR in the impaired fasting glucose/type 2 diabetes group (Supplementary Table 2). In contrast, in the normal fasting glucose group there were significant differences both at 2 years (insulin, P = 0.025, and HOMA-IR, P = 0.031) and at 10 years (insulin, P = 0.045) (Supplementary Table 2).

CONCLUSIONS

This report suggests that within a given weight change class, the changes in fasting insulin and HOMA-IR over 2 and 10 years are similar with banding, VBG, and GBP. In addition, changes in fasting glucose within each weight change class were either similar or even smaller after GBP than after banding and VBG. The glucose and insulin reductions increased with increasing weight loss and were larger in impaired fasting glucose/type 2 diabetes than in patients with normal fasting glucose.

A large number of short-term reports (0.1–4 years) suggest that GBP is more efficient than banding in improving glucose and insulin levels and that GBP causes higher rates of type 2 diabetes remission (reviewed in 6,8,10). Most reports on weight loss–independent effects of GBP on glucose and insulin levels are based on observations a few weeks postoperatively before major

Table 2—Regression slopes (b) for changes in glucose, insulin, and HOMA-IR by 5% weight change in the three surgical groups (banding, VBG, and GBP)

Variable change/year	Banding b-coefficient (95% CI)	VBG b-coefficient (95% CI)	GBP b-coefficient (95% CI)	*P* for test of equal slopes
Glucose				
2-year	0.10 (0.06–0.15)	0.13 (0.10–0.16)	0.09 (0.05–0.14)	0.139
10-year	0.17 (0.12–0.22)	0.19 (0.14–0.24)	0.21 (0.08–0.33)	0.787
Insulin				
2-year	8.00 (5.41–10.60)	7.86 (6.97–8.75)	5.34 (3.51–7.17)	0.091
10-year	8.95 (6.86–11.04)	9.98 (8.20–11.76)	7.13 (2.10–2.17)	0.403
HOMA-IR				
2-year	0.34 (021–0.47)	0.33 (0.29–0.38)	0.21 (0.13–0.28)	0.084
10-year	0.43 (0.32–0.53)	0.48 (0.38–0.58)	0.35 (0.15–0.55)	0.436

weight loss occurred (7,9). Weight reduction occurs faster after GBP than after banding or VBG (4), and even though it is well established that postoperative signaling patterns specific for GBP do exist (19,36,37), a negative energy balance also exists soon after GBP surgery. Indeed, several recent studies indicate that, despite profound changes in gut hormone patterns, pure caloric restriction may cause the short-term metabolic benefits of GBP in obese patients (25,26,28). When comparing GBP to calorie restriction, postprandial glucose levels were improved to a similar extent after both treatments (25,28) and treatment with a very low-calorie diet was as efficient as GBP for improving β-cell function and insulin sensitivity after patients had lost the same amount of weight (26). In patients without type 2 diabetes, it was shown that the improvement in insulin sensitivity was determined by the amount of weight lost—not whether the patients had been treated with GBP or caloric restriction (29). Furthermore, another study of patients without type 2 diabetes showed that effects on insulin sensitivity and β-cell function were similar after GBP and banding after 20% weight loss, occurring after 16 and 22 weeks, respectively (27). Consequently, it is important to investigate whether long-term effects on risk factor changes are similar after GBP compared with restrictive procedures when adequate adjustments for degree of weight loss have been performed.

In the current analyses of 2- and 10-year data from the SOS study, we found that when weight change was adjusted for, GBP was not associated with larger long-term reductions in fasting glucose, fasting insulin, or HOMA-IR than those seen after banding or VBG. This was the case both when analyzing the total cohort and when subgrouping individuals by baseline glucose status. If anything, the reductions in fasting glucose within a given weight change class tended to be of smaller magnitude after GBP. In the SOS study, we previously showed that long-term diabetes remission frequencies are similar in GBP, VBG, and banding groups and that short diabetes duration and high baseline glucose are predictors for both short- and long-term diabetes remission (15). In the current report, we extend our findings by showing that the association between weight change and change in risk factor is similar for the three surgery techniques. However, as shown in the Supplementary Data, the group of patients with impaired fasting glucose or type 2 diabetes is responsible for the major part of the metabolic risk factor changes, whereas changes in the normal fasting glucose group are more modest.

This study has limitations. First, we cannot draw the conclusion that early weight loss–independent effects on glucose and insulin levels after GBP surgery do not exist. In the acute postoperative situation, changes in incretins, insulin, and glucose are no doubt larger after GBP than after banding (7,9). Unfortunately, we are unable to analyze acute weight loss–independent changes in the SOS study, since the first biochemical observations were not collected until 2 years after surgery. Second, different mechanisms affect postprandial (as assessed by glucose tolerance) and fasting plasma glucose levels (38,39). Studies in patients with impaired glucose tolerance have shown that reduced second-phase insulin release and peripheral insulin resistance affect plasma glucose levels. In contrast, patients with impaired fasting glucose suffer from impaired basal insulin secretion and preferential resistance of glucose production to suppression by insulin (38). However, glucose tolerance tests or clamp examinations were not undertaken within the SOS study, making it impossible to draw conclusions on the long-term postprandial effects. Hence, we are unable to analyze whether postprandial glucose changes corrected for weight change are influenced differently by the three surgical techniques. Only fasting measures of insulin and glucose were available, and we therefore used HOMA-IR to estimate insulin resistance. For better understanding of the mechanisms behind changes in insulin sensitivity for different surgical techniques, long-term clamp studies are needed. In the group with normal fasting glucose at baseline, we found that the association between change in insulin and change in weight differed between the surgical groups. The reasons for this are not clear; however, it is possible that the association between insulin and weight is not linear throughout the entire weight loss range. If this were the case, the association would also depend on the absolute magnitude of weight loss and may thereby be different for GBP, which on average results in greater weight loss than the other techniques. In addition, the low participation rate in physical and laboratory examinations at 10 years is a limitation. Finally, the SOS study is a large prospective, controlled intervention study with >2,000 participants in the surgical group. This gives us a unique opportunity to perform detailed analyses on the long-term effects of bariatric surgery. However, the majority (68% [*n* = 1,369]) of the surgical patients in the SOS study underwent VBG, an operation that is rarely performed today, whereas 13% (*n* = 265) of the patients underwent the, at present, most common surgical technique (i.e., GBP). Furthermore, 17% (*n* = 376) of the surgical group underwent banding. This technique is still widely used, but there has been a significant decline in banding rates during the past few years (40).

In conclusion, given the same degree of weight loss after bariatric surgery, there was no support for weight loss–independent benefits of GBP over restrictive procedures on fasting glucose and insulin levels or HOMA-IR over 2 and 10 years. Hence, even though weight loss–independent effects that differ between surgical procedures are important for short-term remission, our results suggest that degree of weight loss is more important for long-term reductions in fasting insulin and glucose than choice of bariatric surgery procedure.

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Author Contributions. K.S., E.S., and M.P. wrote the first version of the manuscript. K.S., L.M.S.C., and M.P. finalized the report. M.P. had principal responsibility for the statistical analyses of the data. All the authors participated in the interpretation of results and have seen, commented on, and approved the final report. L.M.S.C. and M.P. 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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