What is the impact of sleeve gastrectomy and gastric bypass on metabolic control of diabetes? A clinic-based cohort of Mediterranean diabetic patients

Published version:

DOI:10.1016/j.soard.2015.02.017

(Article begins on next page)

What is the impact of sleeve gastrectomy and gastric bypass on metabolic control of diabetes? A clinic-based cohort of Mediterranean diabetic patients

Short Title: The impact of bariatric surgery in real practice

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Acknowledgement: the study was partially supported by Piedmont Region, Italy

Conflicts of interest and source of funding: No potential conflicts of interest relevant to this article were reported

Abstract

Background: effectiveness of sleeve gastrectomy and gastric bypass on glycemic, blood pressure and lipids control in obese type 2 diabetic patients is poorly known.

Objective: to assess effectiveness of bariatric surgery in obese type 2 diabetic people.

Setting: University Hospital, Italy

Methods: Diabetes remission and metabolic changes over post-operative follow-up were assessed in 135 obese patients with type 2 diabetes who underwent bariatric surgery in the 2007-2011 period (gastric bypass, n=100; sleeve gastrectomy, n=35). Repeated-measures analysis of variance and logistic regression were used.

Results: Diabetes remission was observed in 22% and 21.5% of the patients, respectively one and two years after surgery. Compared to the remaining patients, patients in diabetes remission were significantly younger, had lower diabetes duration, hemoglobin A1c (HbA1c), fasting plasma glucose, and frequency of insulin-treatment. Trends of HbA1c, body mass index (BMI), blood pressure, plasma triglycerides showed a significant decrease and the trend of HDL-cholesterol a significant increase over time in both treatment groups (p<0.001). Patients reaching target levels for at least three out of five indicators of intermediate outcomes of care (composite indicator of good diabetes control) were 25.5% at the baseline and 66.1% at final follow-up visit (p<0.001). In logistic regression, age (OR=0.89, 95% CI 0.84-0.95), HbA1c (OR=0.67, 95% CI 0.49-0.91) and diabetes duration (OR=0.87, 95% CI 0.77-1.00) were independent predictors of diabetes remission.

Conclusions: bariatric surgery is an effective approach to optimize glucose, lipids and blood pressure control in obese type 2 diabetic subjects. Bariatric surgery should be offered earlier over the natural course of diabetes to increase the likelihood of diabetes remission in obese patients.

Keywords: Bariatric surgery, diabetes, blood pressure, lipids

Introduction

Diabetes has reached epidemic proportions in several countries, including United States, China, and India[1-3] and the disease imposes large economic burdens on national health care systems[4]. The attributable risk of obesity on diabetes is 80-90%[1] and tackling obesity epidemic may have a beneficial impact on diabetes burden. Intervention trials have shown that physical activity and other lifestyle changes are effective in reducing the risk of diabetes[5], but effectiveness of these approaches at community level is scarce. Moreover, a recent study performed in overweight and obese diabetic patients has shown that an intensive lifestyle intervention focusing on weight loss only resulted in 6% body weight reduction and failed to reduce cardiovascular morbidity and mortality[6].

Randomised trials have shown that surgical treatment of obesity leads to greater body weight loss and diabetes remission rate than non-surgical approaches[7-9]. Weight loss surgeries have also beneficial glycemic effects that are independent of body weight likely due to favorable changes in gut hormone secretion[10]. Although bariatric surgery is emerging as the most effective treatment for selected obese diabetic subjects, studies supporting a more extensive use of surgical approaches in obese diabetic patients have several limitations, such as the low number of studied subjects and the short duration of follow-up[11-17]. Furthermore, there is little information on the metabolic effects of laparoscopic sleeve gastrectomy (stand-alone operation) that is emerging as an especially attractive procedure for high-risk patients[18-20]. Therefore, further studies are required to confirm promising findings and to prompt diabetologists to overcome clinical inertia and consider surgery as a reasonable and attractive therapeutic option in selected obese diabetic patients.

In this study, we assessed the effectiveness of gastric bypass and sleeve gastrectomy on the durability of glycemic, blood pressure, and lipids control in a Mediterranean clinic-based cohort of obese patients with type 2 diabetes.

Materials and Methods

The study base included all consecutive type 2 diabetic obese patients who underwent bariatric laparoscopic surgery between 1 January 2007 and 31 December 2011 at the regional reference Centre of Bariatric Surgery of the Turin University[21], covering a catchment area of almost 5 millions of inhabitants. The number of recruited patients was greater in 2011 because of the publication in 2010 of a Consensus Statement (Italian Diabetes Society) recommending bariatric surgery in selected obese diabetic patients.

Type 2 diabetes was defined as fasting plasma glucose ≥ 126 mg/dl or diabetes medication use (insulin, oral antidiabetic drugs, or both) according to international criteria[22-23]. The inclusion criteria were an age of 25 to 70 years and a body mass index (BMI) ≥ 35 kg/m^2. The exclusion criteria were: pregnancy; severe inflammatory, neurologic or cardiovascular diseases; malignancy; contraindications to obesity surgery or unacceptable surgical risks. All patients provided a written informed consent.

After surgery, each patient underwent follow-up visits every 12 months and both clinical and laboratory data were recorded. Diabetes specialists and registered dieticians assessed glycemic, blood pressure, and lipid control and adjusted treatment according to international guidelines[22-23]. A final follow-up examination was performed in 2012 to assess survival and review medical records. The interval from surgery to the final follow-up examination was of at least 12 months in all patients. Out of the 140 recruited patients two patients died (stroke; accident) and 3 patients moved to another Italian Region during the follow-up period; therefore, 135 patients with clinical and metabolic data were available for the analyses. Because of the open cohort study design, lengths of follow-up varied among patients: 1 year follow up (n=135), 2 years follow up (n=56), 3 years follow up (n=46), 4 years follow up (n=35), 5 years follow up (n=23).

The outcome measures were percent excess weight loss, a composite indicator of good diabetes control (GDC) and diabetes remission. Percent excess weight loss was calculated as [(operative weight-ideal weight)/(operative weight – ideal weight)]*100 with ideal weight based on BMI of 25 kg/m^2. A composite indicator of GDC based on international guidelines[22-23] was calculated, assigning a score of 1 for each item (maximum score=5) defining the achievement of good glucose (HbA1c values lower than 7%), blood pressure (values below 130/80 mmHg) and lipids control (values of LDL-cholesterol <100 mg/dl, triglycerides <150 mg/dl, HDL-cholesterol >40 mg/dl in men and >50 mg/dl in women). Diabetes remission was defined as hemoglobin A1c (HbA1c) ≤ 6.0% (42 mmol/mol) and no diabetes medications[24].

Statistical analysis

Normally distributed baseline variables were reported as mean and standard deviation (SD), while variables with a skewed distribution (triglycerides, creatinine) were analyzed after logarithmic transformation and data reported as geometric means and interquartile range (IQR). Comparisons were performed using the Student t test and the χ^2 test as appropriate. Repeated-measurement ANOVA was used to assess individual changes in HbA1c, BMI, blood pressure, lipid levels during follow-up visits scheduled every 12 months after surgery. A conservative F-test was employed to analyse the interaction between time and treatment. The Greenhouse-Geisser correction for the F test was used to adjust the degrees of freedom for deviations form sphericity (one of the assumptions of repeated-measures analysis of variance). Percent excess weight loss and the composite indicator of GDC were calculated at the final examination. Diabetes remission was assessed in subjects with a minimum follow up period of 12 and 24 months. Logistic regression analysis was used to estimate the odds ratios (ORs) of diabetes remission, independently of confounders and known risk factors. Both backward and forward strategies examining all explanatory variables were employed to select models. The likelihood ratio test was used to compare nested models examining the role of baseline age, sex, diabetes duration, BMI, HbA1c, systolic and diastolic blood pressure, creatinine, diabetic treatment (diet, oral drugs, insulin), and percent excess weight loss. Variables were retained in the final model if they added significantly to the likelihood of models or to the estimated coefficients of predictors. All P values were 2-sided, and P values of less than 0.05 were considered statistically significant. STATA version 10.0 was used for the analyses.

Results

As shown in Table 1, mean baseline age of recruited patients was 49.0 ± 9.3 years (IQR 42.4-57.2 years) and most of them were women (74%). Mean duration of diabetes was 8.2 years (IQR 3-10 years) and 25.9% of patients were treated with insulin. Baseline glycemic control was poor (HbA1c >7.0%) in 58% of patients and 25% of them had HbA1c values ≥ 9.5%. BMI was >44.9 kg/m^2 (IQR 40.3-49.8) in 50% of the patients and only six patients had values of 32.7-34.9 kg/m^2. Blood pressure levels above 130/80 mmHg were found in 49.9% of patients and 68.1% of the subjects had arterial hypertension. Baseline characteristics were similar in patients who underwent gastric bypass (n=100) and sleeve gastrectomy (n=35) (Table 1).

At the final examination, percent excess weight loss was 58.7 ± 24.0 and it was comparable in patients treated with gastric bypass and sleeve gastrectomy (61.2±26.5 vs. 52.3 ± 23.0, p=0.09).

Figure 1 shows trends of HbA1c, BMI, blood pressure, plasma triglycerides, and HDL-cholesterol levels over time. There a statistically significant decrease in HbA1c, BMI, blood pressure, plasma triglycerides over time, while HDL-cholesterol significantly increased (p<0.001). Patients who underwent sleeve gastrectomy had a shorter length of follow up; however, no differences were observed between treatment groups during this time period.

A composite GDC score ≥ 3 was achieved by 25.5% and 66.1% patients (p<0.001) at baseline and final examination, respectively. Percentage of patients requiring insulin treatment decreased from 25.9% to 9.6% (p<0.001). Remission of diabetes was observed in 22% and 21.5% of the patients, respectively one and two years after surgery. There were no significant differences in diabetes remission between the gastric bypass group and the sleeve gastrectomy group (n=21/100 vs n=8/35, p=0.92). As shown in Table 2, diabetic patients in remission had younger age (p=0.001), shorter diabetes duration (p=0.001), lower HbA1c (p=0.01) and fasting plasma glucose levels (p=0.03) at baseline. In patients with longer follow-up length, diabetes remission sustained and no cases of diabetes relapse were observed.

Logistic regression analysis was also performed to assess variables independently associated with the likelihood of diabetes remission. Younger age (OR=0.89, 95% CI 0.84-0.95), lower HbA1c (OR=0.67, 95% CI 0.49-0.91) and diabetes duration (OR=0.87, 95% CI 0.77-1.00) were independent predictors of diabetes remission, whereas other examined variables (percent excess weight loss, BMI, treatment for diabetes, lipids and blood pressure) did not modify estimated ORs.

Conclusions

Our study showed that one out of five Mediterranean type 2 diabetic patients who underwent bariatric surgery had complete remission of diabetes, defined as HbA1c values <6% and no use of diabetic medications. Furthermore, most of the remaining patients showed a decreasing trend of BMI, blood pressure, plasma lipids and medication use over time, indicating an overall metabolic benefit of surgical treatment. Consistently, 66.1% of patients reached target levels for at least three out of five indicators of intermediate outcomes of care (HbA1c, blood pressure, LDL-cholesterol, HDL-cholesterol and triglycerides), while this was achieved by only 25.5% patients prior to bariatric surgery. This finding is of particular relevance as there is convincing evidence that multifactorial treatment of cardiovascular risk factors is mandatory to reduce diabetes complications and mortality[25]. Optimal metabolic control is seldom achieved in obese diabetic patients; therefore, the improvement in metabolic control after bariatric surgery, herein reported, appears quite striking. Finally, performance of sleeve gastrectomy and gastric bypass were comparable in our study, suggesting that sleeve gastrectomy may be effective as a stand-alone bariatric operation in diabetic people. However, these data should be considered with caution, due to the limited numbers of patients who underwent sleeve gastrectomy in our cohort.

Our findings are consistent with those reported in recent clinical trials comparing bariatric surgery and intensive medical therapy alone. However, our data not only show a beneficial metabolic effect of bariatric surgery in diabetic patients, but importantly confirm clinical effectiveness in unselected patients[11-16]. It is noteworthy that mean diabetes duration was longer than in previous studies, suggesting that in our clinical setting obese patients are delayed from undergoing bariatric surgery even after diabetes diagnosis, thus hampering the likelihood of a complete restoration of β-cell function. However, most of diabetic patients of our cohort improved metabolic control after surgery and often switched from insulin to oral treatment with a likely favourable impact on the quality of life.

Bariatric surgery is emerging as the most effective therapeutic approach for obese patients with diabetes. The largest observational cohort of obese diabetic patients undergoing bariatric surgery was part of the Swedish Obese Subjects (SOS) study. In this cohort, however, most of the patients underwent vertical banded gastroplasty and only 55 patients had a gastric bypass. Over 10-years of follow-up bariatric surgery was associated with greater diabetes remission rate[15] and, importantly, the risk of micro- and macrovascular complications was reduced by 60% and 30%, respectively[15]. Other studies have also provided evidence of a substantial reduction in health care utilization and direct healthcare costs, thus confirming the cost-effectiveness of bariatric surgery[26-27].

Consistent with previous studies, we found that diabetes remission is independent of weight loss. Indeed, in our logistic regression analysis, younger age, higher values of HbA1c, and a shorter diabetes duration were independently associated with the likelihood of diabetes remission, while neither pre-operative BMI nor excess weight loss had a predictive value. This finding has clinical implications, suggesting that the bariatric surgery should be offered earlier in the natural course of the disease, probably at diabetes diagnosis, to increase the likelihood of obtaining complete remission. According to recent guidelines, qualification for bariatric surgery includes: BMI 35-40 kg/m^2 and the presence of co-morbidities as surgically-induced weight loss is expected to improve underlying obesity-related disorders[28]. Unfortunately, there is little evidence-based information on the effectiveness of bariatric surgery in diabetic patients with BMI≥30 and <35 kg/m^2 and in this subgroup of patients indication for bariatric surgery should be individually assessed[29]. Recently, a favourable metabolic response to gastric bypass has also been reported in non-obese diabetic Asian patients[30], however, further studies are required to confirm these promising findings.

Our study has several limitations. First, this is an observational study from a single referent academic clinic for bariatric surgery and there was not a control group of obese diabetic patients. However, all consecutive patients who underwent bariatric surgery over the study period were included in the study, thus allowing to exclude selection bias effects, and patients were representative of obese diabetic patients in Italy allowing the results to be generalized to other patients. Second, the number of recruited subjects was relatively small, particularly in the group who underwent sleeve gastrectomy. Third, data on annual examinations were retrospectively obtained from medical records. However, high completeness of ascertainment of data was obtained, thus allowing to limit detection bias. Furthermore, all patients were regularly assessed in the diabetic clinic using standardized laboratory and clinical procedures, thus limiting the effect of observational bias. Finally, the follow-up period for patients who underwent sleeve gastrectomy was limited to 3 years. However, previous data on the metabolic effects of sleeve gastrectomy in diabetic patients are quite scarce and our study adds to the existing knowledge in this area.

Our study has also considerable strengths, such as the centralization of all laboratory measurements, the high degree of completeness of ascertainment at the follow-up examination and the assessment of the effectiveness of surgical procedures in the setting of clinical practice. Finally, data were analysed using repeated-measurement ANOVA with fixed time intervals and this allows, at variance with previous studies, to take into account the effect of individual variability over time. Therefore, internal and external validity of our data allow to generalize our conclusions to the obese diabetic population.

In conclusion, our study showed that bariatric surgery is effective in reducing the cardiovascular risk profile of diabetic patients and in achieving diabetes remission. However, the likelihood of remission was higher in younger patients with lower diabetes duration, suggesting that surgical procedures should be suggested earlier over the natural course of the disease.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest and source of funding: No potential conflicts of interest relevant to this article were reported. **Informed consent:** Informed consent was obtained from all individual participants included in the study.

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Table 1: Baseline features of the clinic-based cohort of diabetic patients who underwent bariatric surgery, by surgical procedure

Table 2: Baseline features of the clinic-based cohort of diabetic patients who underwent bariatric surgery, by diabetes remission

Legend Figure 1: Pattern over time of HbA1c (A), BMI (B), systolic and diastolic blood pressure (C,D), plasma triglycerides (E) and HDL-cholesterol (F), by bariatric procedure in the cohort of 135 eligible patients out of 140 patients who underwent bariatric surgery and were regularly assessed at the annual follow-up visit (gastric bypass, solid line, n=100; sleeve gastrectomy, dotted line, n=35). Lengths of follow-up varied among patients: 1 year follow up (n=135), 2 years follow up (n=56), 3 years follow up (n=46), 4 years follow up (n=35), 5 years follow up (n=23).