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ORIGINAL CONTRIBUTIONS

Prediction of Diabetes Remission at Long Term Following Biliopancreatic Diversion

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Abstract
Importance In obese patients with type 2 diabetes (T2DM), the marked weight loss following bariatric surgery is accompanied in a consistent number of cases by T2DM resolution or control. The clinical need of preoperative parameters reliable in predicting a positive metabolic outcome at long term following the operation has then emerged.
Observation A cohort of 135 consecutive T2DM patients with a wide range of body mass index (BMI) at more than 5 years following biliopancreatic diversion (BPD) was considered. The 5-year-T2DM resolution, defined as glycosylated hemoglobin ($HbA1_C$) lower than 6.5% without antidiabetic therapy, was related to demographic, anthropometric, and biochemical findings prior to the operation. The long-term metabolic outcome was positively related to baseline BMI values and negatively with the preoperative use of insulin.
Conclusion BMI and insulin therapy at the time of surgery are associated with the probability of T2DM long lasting remission and could be used as solid predictors before surgery. In the overweight and non morbidly obese diabetic patients, bariatric surgery is less efficient in determining long term T2DM resolution than in their morbid obese counterparts.

Keywords Baritatric surgery · Type 2 diabetes · Obesity

Introduction

Bariatric surgery has been actively an investigated therapy for type 2 diabetes (T2DM) in morbid obesity; long term diabetes remission today is representing the primary target of bariatric surgery [1, 2]. Rates of T2DM remission depend both on the type of operation utilized (biliopancreatic diversion being the most powerful) and on clinical characteristics of the patients (BMI, age, diabetes duration, insulin therapy among others). Since a significant reduction of blood glucose is commonly observed before a meaningful weight loss, a metabolic effect of bariatric surgery also in lean or overweight subjects has been proposed [3, 4, 6]. Based on this background, surgery was performed, in experimental settings, in overweight or grade I obesity patients with T2DM, but the rates of diabetes remission were lower than those previously observed in subjects with higher BMI, challenging the concept of a antidiabetic effect of surgery independent of BMI [5] Nevertheless, an increasing number of patients, with a wide range of BMI, is looking for surgery to cure T2DM, and the possibility of a reliable forecast of the chance of remission of diabetes after surgery would be very useful to select patients for surgery.

The aim of this work was to identify predictors of T2DM remission, combining easily to obtain anthropometric, demographic, and clinical variables before the operation. With this aim, we carried out a retrospective analysis in a cohort of patients with T2DM and a wide range of BMI having undergone biliopancreatic diversion (BPD) with a follow-up of 5 years.

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Table 1 Patients with type 2 diabetes (T2DM) at various body mass index (BMI) level undergoing biliopancreatic diversion; demographic, anthropometric and clinical data are recorded prior to the operation

Cases	135
Age (years)	52 ± 9.5
Gender (m/f)	82/53
T2DM duration (years)	11.1 ± 7.8
Insulin therapy (# and %)	53 (39%)
Body weight (mean ± ds, hg)	104 ± 28.4
Body mass index (mean ± ds, kg/m^2)	27.0 ± 9.6
Fasting blood glucose (mean ± ds, mg/dl	220 ± 85
HbA1c serum concentration (%)	9.17 ± 1.74

HbA1c glycated hemoglobin

Material and Methods

This analysis was carried out on consecutive patients with T2DM having undergone laparoscopic BPD with standard technique [6] for T2DM treatment between September 2007 and June 2010 at the department of Surgery of the University of Genova. All patients had received a diagnosis of diabetes from at least 2 years and were on an antidiabetic treatment. Postoperative morbidity and mortality were fully in line with those described in larger cohorts of diabetic and not diabetic obese patients [6]. This cohort is composed by subjects with T2DM and BMI ranging from 27 to >40, who had been included in prospective studies on BPD metabolic effects [7]. Clinical follow-up was carried out yearly for 5 years and included physical and standard biochemical examinations. The overall follow-up rate was 82% at 5 years. Patients without follow-up information at 5 years were excluded from the analysis. A glycosylated hemoglobin (HbA1C) lower than 6.5% without antidiabetic therapy in the last 6 months was

Table 2 Patients with type 2 diabetes (T2DM) at various body mass index (BMI) level undergoing biliopancreatic diversion (BPD). Univariate and multivariate logistic model where the 5-year post-BPD T2DM remission is the dependent variable, and the independent variables are categorized

	n	5-year-remissions (%)	Univariate analysis		Multivariate analysis	
			OR (95% CL)	*P*	OR (95% CL)	*P*
BMI				0.004		0.002
Less than 30 kg/m^2	31	11 (35.5)	Ref		Ref	
30–34.9 kg/m^2	33	18 (54.5)	2.18 (0.80–5.96)		2.18 (0.76–6.27)	
35–39.9 kg/m^2	10	7 (70)	4.24 (0.91–19.78)		3.22 (0.62–16.65)	
40–40.9 kg/m^2	24	20 (83.3)	9.09 (2.47–33.41)		15.32 (2.85–82.45)	
More than >50 kg/m^2	10	9 (90%)	16.36 (1.83–146.66)		8.77 (0.90–85.44)	
T2DM duration				0.026	*	0.834
1–4 years	24	21 (87.5)	Ref		–	
5–10 years	33	20 (60.6)	0.22 (0.05–0.89)		–	
11–19 years	29	13 (44.8)	0.12 (0.03–0.48)		–	
More than 20 years	19	10 (52.6)	0.16 (0.03–0.72)		–	
HBcCat3				0.228	*	0.654
Less than <8%	25	18 (72)	Ref		–	
8–10%	56	29 (51.8)	0.42 (0.15–1.16)		–	
More than 10%	21	13 (61.9)	0.63 (0.18–2.18)		–	
Age				0.22	*	0.402
Less than 46	23	20 (87%)	Ref		–	
46–55	45	25 (55.6)	0.19 (0.05–0.72)		–	
More than 56 years	40	20 (50)	0.15 (0.04–0.59)		–	
Insulin				0.001		0.005
No	66	48 (72.7)	Ref		Ref	
Yes	42	17 (40.5)	3.92 (1.72–8.91		3.71 (1.46–9.41)	
Genere				0.151	*	0.206
F	39	27 (69.2)	Ref		–	
M	69	38 (55.1)	0.54 (0.24–1.25)		–	

*Removed from the final model

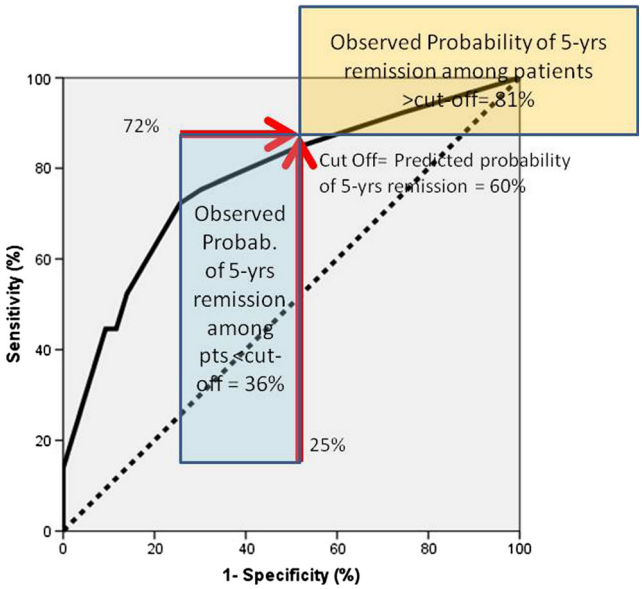

Fig. 1 ROC curve based on the logistic score estimated by logistic regression model with BMI (5 levels) and Insulin use (2 levels) as covariate, and diabetes remission at 5 years, the dependent variable. Sensitivity indicates the proportion of patients experiencing remission who were correctly classified, and specificity refers the proportion of patients not experiencing remission who are correctly classified, at each cut-off of the logistic score. Using a cut-off corresponding to a predicted probability of 60%, sensitivity was 72% and specificity was 72%. The observed probability of remission among patients above and below this cut-off were 81 and 36%, respectively

considered as T2DM remission [8]. The association between diabetes remission and various baseline (preoperative) characteristics including age, gender, diabetes duration, $HbA1_C$, BMI, and anti diabetic therapy were analyzed using univariate analysis (odd ratio with 95% confidential interval and chi square test for homogeneity or trend, as appropriate). In this analysis, all continuous variables were categorized. In order to estimate the probability of remission, a multivariate logistic regression model was fitted to the data including the above mentioned variables as covariates and diabetes remission at 5 years as the dependent variable. All covariates were initially included in the model, and the final model arrived at by means of a step down procedure based on the likelihood ratio test. The probability of diabetes remission estimated by the logistic model was then computed for each individual and compared with the actual occurrence of remission by means of the standard ROC curve. Sensitivity and specificity of the model was then estimated at various cut-offs of the logistic score.

Results

Among the 135 patients with T2DM submitted to BPD, 108 completed the 5-year-follow-up and 27 not (3 patients died, 2 refused the control visit and 22 were lost with a follow-up rate of 85%). In Table 1, the preoperative demographic, anthropometric, and clinical characteristics of the patients are reported. Among the patients who completed the 5-year-follow up, 65 (60.7% of cases) experienced a long-term complete T2DM remission, with below the HbA1c threshold value of 6.5%. At the fifth year follow-up point, all the patients with higher HbA1c level were currently treated with antidiabetic drugs. Univariate and multivariate associations with the probability of remission at 5 years are shown in Table 2. The rate of remission increased with increasing preoperative BMI values and decreased for longer T2DM duration, and the probability of durable remission was lower among the patients treated with insulin prior to the operation, while there were no differences depending on gender, age, and $Hb1A_c$ values at the time of surgery. However, when all these variables were fitted into a multivariable logistic model (Table 2), only preoperative BMI and not using insulin prior to BPD were significantly associated with the probability of remission at 5 years ($p = 0.002$ and $p = 0.005$, respectively). The other variables were removed from the final model (all p values >0.2).

When the probability of diabetes remission estimated by the logistic model using these two variables was computed for each patient and compared in the 5-year-remitters and non remitter patients, the resulting ROC curve (Fig. 1) indicated a satisfactory discrimination with an area under the curve of 0.775 and a sensitivity and specificity at the optimal cut-off (probability of remission = 0.60) of 72 and 75%, respectively. The probability of 5-year-remission among all patients above this cut off was 81% (47/58), while it was 36% (18/50) among patients below this threshold.

Discussion

This retrospective analysis shows that BMI and not using insulin therapy at the time of surgery are associated with the probability of T2DM long lasting remission and could be used as solid predictors before surgery. Although the T2DM post-operative remission rate progressively decreased with the increasing of the T2DM duration prior to BPD, this variable was not independently associated with the 5-year metabolic outcome in multivariate analysis, after adjustment for BMI and insulin therapy. These results are not-in keeping with findings recently obtained by analyzing the preoperative T2DM patients of the Swedish Obese Study (SOS) cohort [9]. In that study, the best predictors of T2DM remission were a shorter T2DM duration with a better baseline glucose control, suggesting that BMI values did not influence the long-term metabolic outcome after bariatric surgery. However, in the SOS study, only patients with preoperative BMI values higher that 35 kg/m^2 were enrolled, making it difficult to detect a relationship between outcome and BMI over a sufficiently ample range of BMI values. Moreover, different types of bariatric operation were performed, and no data on T2DM remission

rates by type of surgery were presented. Based on the available literature data, a far better metabolic result has to be hypothesized in the subjects having undergone Roux-en-Y gastric bypass and BPD than in those submitted to simple gastric restriction procedures, who represented about 70% of population. These two factors may account for the differences between our results and those of the SOS study.

Multivariate logistic regression analysis is allowed to compute a score based on BMI and insulin therapy that was used in a ROC analysis to identify the optimal cut off among T2DM stable remitters and non remitters at long-term following BPD; at 60% of probability of T2DM remission, the patients are predicted with a highly satisfactory level of both sensitivity and specificity (72% and 75%, respectively). Therefore, the T2DM patients with lower baseline BMI level or/or using insulin therapy have to be addressed to bariatric surgery with great caution.

A general consensus exists on two main mechanisms underlying T2DM remission after bariatric surgery: decreased hepatic and peripheral insulin resistance and recovery of beta cell insulin secretion. These effects are more frequently observed in subjects with higher BMI and in diabetic subjects not treated with insulin, most likely for a beta cell damage of lower degree [10] As a consequence, our results perfectly fit current clinical recommendations for the use of bariatric surgery [11], as well as pathophysiology mechanisms. In this morbid obese population with T2DM, BPD might be considered as a true disease modifier.

Compliance with Ethical Standards In this type of study, ethical approval is not necessary.

Conflict of Interest The authors declare that they have no conflict of interest.

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