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C-peptide levels predict type 2 diabetes remission after bariatric surgery

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Abstract

Background: C-peptide (Cp) serves as a surrogate of pancreatic beta-cell reserve. This study evaluates the clinical significance of basal Cp as a predictor of type 2 diabetes (T2D) remission after bariatric surgery (BS).

Research design and methods: Retrospective study of 22 patients with BMI > 35 kg/m² and T2D who underwent BS. Evaluation of anthropometric and glucose metabolism parameters before BS and at one-year follow-up. Analysis of patients with T2D remission (HbA1c < 6%, fasting glucose (FG) < 100 mg/dl, absence of pharmacologic treatment) and preoperative characteristics associated (logistic binary regression model). ROC curve to estimate an optimal Cp value to predict T2D remission.

Results: Preoperatively (mean ± SD): age 53.3 ± 9.4 years, BMI 42.9 ± 6.8 kg/m², T2D duration 6.9 ± 5.2 years, FG 159.6 ± 56.6 mg/dL, HbA1c 7.5 ± 1.1%, Cp 4.0 ± 2.0 (median 3.8, range 0.1-8.9) ng/mL. At one year follow-up, remission of T2D in 12 cases (54.5%). Preoperative Cp correlated with 12-month HbA1c (r = -0.519, p = 0.013). Preoperative Cp was higher in those who achieved remission: 5.0 ± 1.7 vs 3.0 ± 1.7 ng/ml, p = 0.013. A Cp concentration > 3.75 ng/mL provided a clinically useful cut-off for prediction of T2D remission. T2D remission rates were different according to median preoperative Cp: 27.3% if Cp < 3.8 ng/mL and 81.7% if Cp > 3.8 ng/mL (p = 0.010).

Conclusions: Patients with elevated preoperative Cp levels achieve higher rates of T2D remission one year after BS. A Cp concentration > 3.75 ng/mL seems clinically useful.

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Key words: Bariatric surgery. Metabolic surgery. C-peptide. Diabetes mellitus. Type 2 diabetes mellitus.

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EL PÉPTIDO C PREDICE LA REMISIÓN DE LA DIABETES MELLITUS TIPO 2 TRAS CIRUGÍA BARIÁTRICA

Resumen

Introducción: La determinación del péptido C (pC) suele emplearse como un indicador de la reserva beta-pancreática. El objetivo de este estudio es evaluar si el pC basal, es un parámetro predictor de remisión de diabetes mellitus tipo 2 (DM2) tras cirugía bariátrica (CB).

Material y métodos: Estudio retrospectivo de 22 pacientes con DM2 e IMC > 35 kg/m², intervenidos mediante CB. Recogida de datos clínicos, antropométricos y analíticos relativos al metabolismo de la glucosa, antes de la CB y al año. Análisis de pacientes en remisión completa de DM2 al año de la CB (glucosa basal [GB] < 100 mg/dl, HbA1c < 6%, sin tratamiento farmacológico) y las variables preoperatorias asociadas a remisión (regresión logística binaria). Estimación del mejor valor umbral de pC para predecir la remisión de DM2 con curva ROC.

Resultados: Características pre-CB (media ± DE): edad 53,3 ± 9,4 años, IMC 42,9 ± 6,8 kg/m², duración DM2 6,9 ± 5,2 años, GB 159,6 ± 56,6 mg/dl, HbA1c 7,5 ± 1,1%, pC 4,0 ± 2,0 (mediana 3,8, rango 0,1-8,9) ng/ml. 12 pacientes (54,5%) presentaron remisión de DM2. El pC preoperatorio se correlacionó con la HbA1c a los 12 meses (r = -0,519, p = 0,013). Los valores de pC pre-CB fueron más elevados en los pacientes que alcanzaron remisión de DM2 (5,0 ± 1,7 vs 3,0 ± 1,7 ng/ml, p = 0,013). Un valor de pC > 3,75 ng/ml supuso una sensibilidad y especificidad para remisión de DM2 de 75% y 80%, respectivamente. La tasa de remisión de DM2 fue de 27,3% si el pC basal pre-CB < 3,8 ng/ml, y 81,7% si > 3,8 ng/ml (p = 0,010).

Conclusiones: Los pacientes con pC basal preoperatorio elevado son los que mayores tasas de remisión alcanzan al año de la CB. Una concentración de pC basal > 3,75 ng/dL parece un buen predictor de remisión completa de DM2 al año de la CB.

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Palabras clave: Cirugía bariátrica. Cirugía metabólica. Péptido C. Diabetes mellitus. Diabetes mellitus tipo 2.

Abbreviations

BMI: Body mass index.

%WL: Percentage weight loss.

Introduction

Bariatric surgery (BS) has proved to be effective for achieving a substantial and durable weight loss, as well as for remission of type 2 diabetes (T2D),¹ and, consequently, several national and international guidelines and consensus statements have addressed the indications for BS in patients with T2D.^{2,3} However, T2D remission rates observed across published reports have varied, mainly due to heterogeneity in its definition criteria and patients' preoperative characteristics. In this setting, several preoperative factors have been identified as potential predictors of T2D remission, such a short duration of the disease, no previous insulin use, younger age, and greater weight loss.^{4,6}

C-peptide levels are a surrogate of pancreatic beta-cell mass and insulin secretion, and have been, thus, used for diabetes classification.⁷ Additionally, evaluation of preoperative basal C-peptide has been suggested as a possible predictor of T2D remission after BS.^{8,9} However, its clinical relevance has not been studied clearly in the surgical context.

This study aims to evaluate the clinical significance of C-peptide levels in T2D patients who underwent BS and its role in predicting remission.

Materials and methods

Study population

We conducted a retrospective study of 22 patients who underwent BS in a single center (10 women; mean age 53.3 years, range 33-68) with medication-controlled T2D, defined according to current ADA guidelines.¹⁰ Cases that suggested late-autoimmune diabetes (LADA), a history of type 1 diabetes, maturity-onset diabetes of the young (MODY) and diabetes secondary to a specific disease were excluded.

Information was obtained from medical charts prior to BS and at one-year follow-up. Data collected included: hypoglycemic treatment used, duration of diabetes, anthropometric characteristics (height, weight, body mass index [BMI], calculated as weight (kg)/height (m²), percentage weight loss [%WL] and percentage excess weight loss [%EWL]),¹¹ and glucose metabolism parameters (fasting glucose [FG], glycosylated hemoglobin [HbA1c] and basal C-peptide). Baseline biochemical measures were collected after a minimum 12-hour fasting period, and all assays were performed in the same single accredited laboratory. C-peptide levels were analyzed if FG values were < 200

mg/dL, with IMMULITE 2000 C-peptide (Siemens®) assay (reference range 0.1-20 ng/mL).

All patients signed a written informed consent prior to surgery in which they agreed to the potential use for investigation and publication, in an anonymous way, of clinical and analytical data collected before the bariatric procedure and during follow-up. This study was approved by the Ethics Committee of the Hospital Clinico San Carlos and was in compliance with the Helsinki Declaration.

Definition of diabetes remission

Complete diabetes remission was defined according to the criteria proposed by a consensus group of experts, addressed by the American Diabetes Association (ADA):¹² HbA1c < 6% and FG < 100 mg/dL, in the absence of active pharmacologic treatment.

Surgical procedures

All surgeries were performed laparoscopically, using three types of procedures: Roux-en-Y gastric bypass (RYGB) in 4 patients (18.2%), biliopancreatic diversion (BPD) in 13 (59.1%), and 5 patients (22.7%) underwent sleeve gastrectomy (SG). Eligibility for each of them varied according to the patients' previous diabetes medical history and comorbidities, which was evaluated by the treating physician (endocrinologist and/or surgeon).

Statistical analysis

Descriptive results were expressed as mean ± standard deviation and (range) for continuous variables. Categorical variables were summarized as frequencies and percentages. Preoperative features were examined for their influence on diabetes remission using analysis of variance and Chi Square tests (Fisher's exact test as required). Binary logistic regression analyses were conducted for preoperative characteristics to determine predictors of T2D remission. Pearson's bivariate correlations were performed for all variables. Receiver operating characteristic (ROC) curve was used to provide cut-off values for preoperative C-peptide with the optimal combination of sensitivity and specificity. The p-values were two-sided and statistical significance was considered when $p < 0.05$. All statistical analyses were performed using SPSS version 19.0 (IBM SPSS Statistics Inc., Chicago, IL, USA).

Results

Baseline characteristics were: BMI 42.9 ± 6.8 (33.4-52.9) kg/m², duration of T2D 6.9 ± 5.2 (0.5-20) years,

Table I
Patient's characteristics according to the type of BS performed

	Type of bariatric surgery				P
	All patients	RYGB	BPD	SG	
N° of patients	22	4 (18.3)	13 (59.0)	5 (22.7)	
Women	10 (45.5)	3 (75.0)	4 (30.8)	3 (60.0)	0.227
Age (years)	53.3 ± 9.4	53.8 ± 5.5	54.4 ± 10.1	50.0 ± 10.8	0.566
Previous insulin use	13 (59.1)	3 (75.0)	7 (53.8)	3 (60.0)	0.753
Diabetes duration (years)	6.9 ± 5.2	8.8 ± 8.1	6.5 ± 5.0	6.0 ± 2.9	0.851
Preop-BMI(kg/m ²)	42.9 ± 6.8	35.7 ± 2.6	44.3 ± 7.2	45.1 ± 3.9	0.057
Preop-FG (mg/dL)	159.6 ± 56.6	134.0 ± 40.1	178.2 ± 63.2	132.0 ± 30.6	0.246
Preop-HbA1c (%)	7.5 ± 1.1	7.1 ± 0.9	7.8 ± 1.2	7.1 ± 0.6	0.540
Preop-C-peptide (ng/mL)	4.0 ± 2.0	3.4 ± 0.7	4.8 ± 1.9	2.7 ± 2.3	0.090
12m-BMI(kg/m ²)	27.4 ± 4.7	24.1 ± 1.2	27.1 ± 4.7	31.1 ± 4.6	0.110
12m-FG (mg/dL)	98.4 ± 22.4	92.5 ± 14.4	94.2 ± 20.2	114.0 ± 29.4	0.242
12m-HbA1c (%)	5.4 ± 0.7	5.9 ± 0.7	5.1 ± 0.5	6.0 ± 0.8	0.009
12m-C-peptide (ng/mL)	1.7 ± 1.0	2.9 ± 1.2	1.4 ± 0.4	1.7 ± 1.3	0.036
%WL	35.7 ± 8.2	32.3 ± 5.5	38.5 ± 8.2	31.1 ± 8.0	0.157
%EWL	78.5 ± 18.0	87.7 ± 10.0	81.5 ± 17.4	63.3 ± 18.0	0.148

Values show mean ± SD or number of patients and percentages of the column (%).

Preop = Preoperative; 12m = 12-month; BMI = Body mass index; FG = Fasting glucose; HbA1c = Glycosylated hemoglobin; %WL = Percentage body weight loss at 12 months; %EWL = Percentage excess body weight loss at 12 months.

p-values are shown for Chi-square test (categorical values) and analysis of variance (continuous variables).

FG 159.6 ± 56.5 (77.0-313.0) mg/dL, HbA1c 7.5 ± 1.1 (6.0-9.8) % and basal C-peptide 4.0 ± 2.0 (median 3.8; range 0.1-8.9) ng/mL. Insulin was used by 13 patients (59.1%). There were certain differences in preoperative characteristics according to the type of bariatric procedure performed, but no statistical significance was reached (table I).

One year after BS, anthropometric and laboratory parameters were: BMI 27.4 ± 4.7 kg/m² (%WL 35.7 ± 8.2%, %EWL 78.5 ± 18.0%), FG 98.4 ± 22.4 mg/dL and HbA1c 5.4 ± 0.7%, which were different from preoperative values (p < 0.001 in all cases). Patients who underwent BPD achieved the lowest 12-months' HbA1c levels: 5.1 ± 0.5%, vs 5.9 ± 0.7% in RYGB and 6.0 ± 0.8% in SG, p = 0.009. There were no differences in %WL or %EWL between the three types of BS. C-peptide levels at 12-months' follow-up were 1.7 ± 1.0 ng/mL, which meant a mean reduction of 45.2% (p < 0.001). Patients who underwent RYGB maintained the highest C-peptide levels: 2.9 ± 1.2 ng/mL vs 1.4 ± 0.4 ng/mL in BPD and 1.6 ± 1.3 ng/mL in SG, p = 0.036 (table I). Postoperative C-peptide levels correlated with %WL at 12 months (r = -0.531, p = 0.011) (fig. 1).

T2D complete remission one year after BS was achieved by 12 patients (54.5%). Preoperative C-peptide levels correlated with HbA1c levels at 12 months' follow up (r = -0.519, p = 0.013) (fig. 2); they were higher in those who achieved remission in comparison to those who did not: 5.0 ± 1.7 vs 3.0 ± 1.7 ng/mL, p = 0.013 (fig. 3). Crude odds ratios (OR) and 95% confidence intervals (CI) of preoperative C-peptide and insulin treatment for prediction of T2D remission were 2.256 (95% CI 1.045-4.872), p = 0.038, and 0.056 (95% CI 0.005-0.606), p = 0.018, respectively, reflecting that higher preoperative C-peptide levels and the absence of

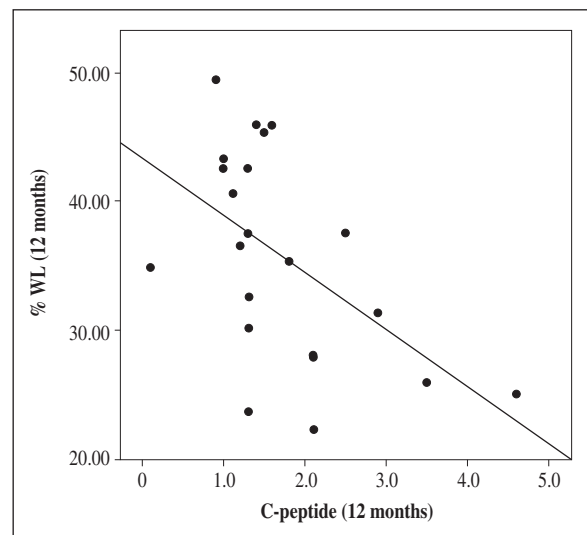


Fig. 1.—Correlation between C-peptide levels at 12 months' follow up and percentage weight loss (%WL) in that period of time.

previous insulin treatment favored T2D remission after BS. After adjusting for different models, statistical significance of preoperative C-peptide and T2D remission was not maintained, although a trend for the influence of preoperative C-peptide could be observed (table II). Considering only patients with previous insulin therapy, preoperative C-peptide levels were higher in those who achieved T2D remission, in comparison to those who did not: 6.2 ± 2.1 vs 2.5 ± 1.2 ng/mL, p = 0.009, but differences in patients with preoperative oral hypoglycemic agents could not be calculated due to insufficient number of cases.

T2D remission rates for patients with preoperative C-peptide levels < 3.8 ng/mL and > 3.8 ng/mL were

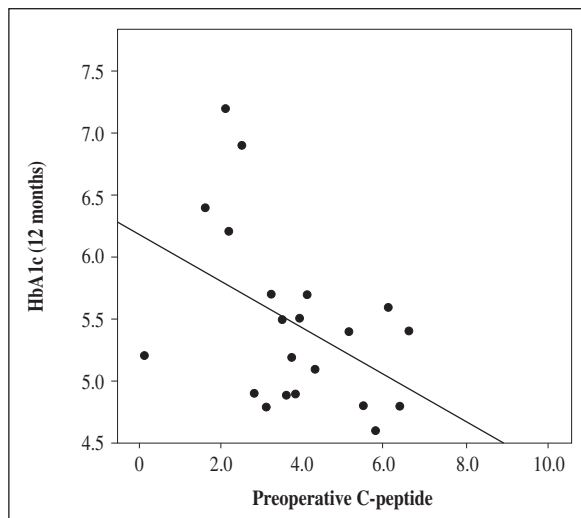


Fig. 2.—Correlation between preoperative C-peptide levels and HbA1c levels at 12 months' follow-up.

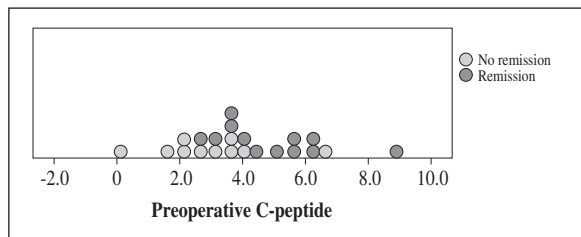


Fig. 3.—Preoperative C-peptide levels according to T2D remission status.

27.3% and 81.7%, respectively, $p = 0.010$ (fig. 4). Selection of the best combination of sensitivity and specificity for preoperative C-peptide levels derived from ROC curve selected a basal preoperative C-peptide value of 3.75 ng/mL, for a sensitivity of 75% and specificity of 80% (AUC 0.808), as a useful cut-off for prediction of T2D remission.

Discussion

BS has proved to be effective for resolution of T2D across numerous different reports,¹ yet different remission rates have been reported due to heterogeneity in criteria for definition of T2D remission and patient's preoperative characteristics.

In order to overcome this variability, several studies have attempted to identify preoperative factors that would potentially be useful as predictors of T2D remission, and, thus, provide a more realistic view of what to expect regarding BS outcomes in different groups of patients.^{6,9} Some of these factors have been consistently observed across different reports. For instance, poorly controlled diabetes, long duration and insufficient weight loss have been witnessed to be associated to lower remission rates.^{4,13}

However, the role of preoperative C-peptide levels after BS has been less extensively explored. C-peptide is

Table II
Odds ratios (OR) and 95% confidence intervals (CI) for preoperative C-peptide levels ant T2D remission, using different models.

Preoperative characteristic	OR	95% CI	p
C-peptide (model 1)	2.193	1.020-4.714	0.044
C-peptide (model 2)	2.157	0.989-4.706	0.053
C-peptide (model 3)	2.258	0.989-5.160	0.053
C-peptide (model 4)	2.015	0.920-4.413	0.080
C-peptide (model 5)	2.141	0.937-4.891	0.071
C-peptide (model 6)	1.899	0.920-3.918	0.083

Model 1: Adjusted for age; Model 2: Adjusted for age and sex; Model 3: Adjusted for diabetes duration; Model 4: Adjusted for previous insulin treatment; Model 5: Adjusted for age and diabetes duration; Model 6: adjusted for age and previous insulin treatment.

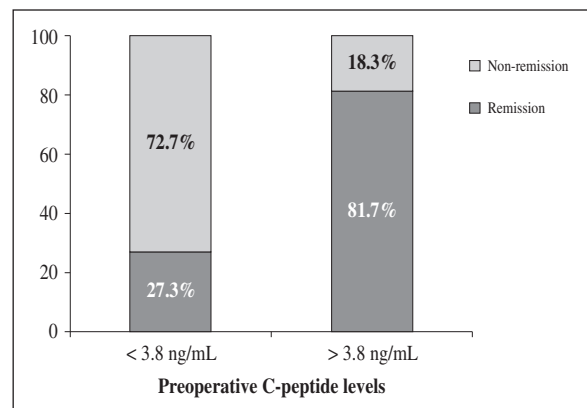


Fig. 4.—Percentage of patients with T2D remission and non-remission according to preoperative C-peptide levels (3.8 ng/mL taken as the median value of the study population).

a valuable test for diabetes classification, as it is a surrogate of pancreatic beta-cell mass and insulin secretion.⁷ High preoperative levels would reflect an intact pancreatic reserve with a suitable compensatory increase in insulin secretion. C-peptide secretion would progressively decrease as diabetes develops and pancreatic reserve is deteriorated and, thus, knowing preoperative C-peptide values may be useful to predict if T2D remission after BS is achievable, depending on the pancreas' difficulty to recover in the postoperative period.⁸

Our study identified that preoperative C-peptide levels were useful predictors of T2D remission, in agreement with previous studies.^{8,14} Additionally, we detected a significant correlation with postoperative HbA1c levels, supporting this observation. Although some authors have also reported a significant correlation with age and preoperative BMI, reflecting the nature of elevated C-peptide in the setting of metabolic syndrome and insulin resistance, the fact that this relationship was not seen in our patients may have been due to the small number of cases studied. We did find, however, that postoperative C-peptide levels correlated with %WL at 12 months, which is in agreement with the afore-mentioned physiologic

hypothesis: as weight was gradually lost, C-peptide levels decreased. This reflects the physiological adjustment which parallels changes in insulin secretion; when a greater amount of weight is lost, hyperinsulinemia is reduced, revealing an improvement in metabolic syndrome and insulin resistance, and, thus, C-peptide levels will also be reduced, accordingly.

Preoperative C-peptide levels were higher in those patients who achieved T2D remission one year after BS. This supports the theory proposed by others¹⁵ that a better-preserved pancreatic beta-cell reserve would be advantageous for effectively controlling glucose homeostasis after BS. In view of this finding, we suggest evaluating basal C-peptide levels systematically before BS to be able to estimate in a realistic way what to expect regarding T2D remission.

Remission rates were significantly different if we considered C-peptide levels below or above the median value of our population (3.8 ng/mL), in agreement with previous reports⁸. But moreover, our study goes one step further by providing a cut-off value for which the best sensitivity and specificity for prediction of T2D remission would be reached: 3.75 ng/mL. To our knowledge, few reports have attempted to provide such a cut-off value.⁶ The reason for this may be that C-peptide levels are not routinely evaluated in the clinical setting, making availability of data frequently scarce. Also, we must bear in mind that caution is required when assessing C-peptide, because assay results can vary with the methods used and between laboratories¹⁶, and previous hypoglycemic treatment, especially insulin and sulfonylureas, may affect serum measures. However, in our study, the number of cases of previous insulin users was sufficient to be able to compare C-peptide levels in T2D remitters and non-remitters and, still, differences were found, supporting the hypothesis that a high preoperative C-peptide is required to attempt complete glycemic control.

Postoperative C-peptide levels were higher in patients who underwent RYGB compared to the BPD group. Although the number of cases evaluated was not enough to elaborate definitive conclusions, we hypothesize that procedures with a more drastic change in gastrointestinal anatomy would influence gut hormone secretion and, therefore, C-peptide levels.¹⁷ However, on the other hand, patients were not randomized to one of the three bariatric procedures, so those who underwent BPD had slightly higher BMI and worse diabetes control in comparison to RYGB patients, jeopardizing the possibility of drawing conclusions regarding the influence of the type of BS performed. Nevertheless, this was not the main purpose of our study. Further studies evaluating a dynamic testing of C-peptide and beta-cell function (measured by the homeostasis model assessment-HOMA-B), such as after glucagon stimulation, an oral glucose tolerance test, or a mixed meal, should be carried out to clarify this issue. Yet, because of the complexity and difficulty that performing these tests entails, we suggest measurement of basal C-peptide values as a means of obtaining similar information, despite its imperfections.

The main limitation of our study was its retrospective design and the small number of patients included. In spite of this, we emphasize that preoperative C-peptide levels may be useful for prediction of T2D remission after BS and we highlight that it should, therefore, be assessed as part of the overall preoperative evaluation of a potential candidate for this type of surgical intervention.

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