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Original article

## Serum levels of osteopontin predict diabetes remission after bariatric surgery



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### ABSTRACT

**Aim.** – Bariatric surgery has been shown to effectively improve glycaemic control in morbidly obese subjects. However, the molecular bases of this association are still elusive and may act independently of weight loss. Here, our retrospective study has investigated the inflammatory molecule osteopontin (OPN) as a potential predictor of type 2 diabetes mellitus (T2DM) remission.

**Methods.** – Baseline serum levels of OPN were analyzed in 41 T2DM patients who underwent bariatric surgery. Anthropometric measures and biochemical variables, including insulin sensitivity indices (HOMA2), were assessed at baseline and at 1 and 3 years after surgery.

**Results.** – At baseline, patients who experienced T2DM remission had increased waist circumference, body weight and BMI, and higher serum OPN, compared with non-remitters. Patients with and without T2DM remission improved their lipid and glucose profiles, although insulin resistance indices were only improved in the T2DM remission group. In the overall cohort of both T2DM remission and non-remission patients, baseline circulating levels of OPN significantly correlated with reductions of body weight and BMI over time, and insulin sensitivity improved as well. However, only the HOMA2-%S remained independently associated with serum OPN on multivariate linear regression analysis (B: 0.227, 95% CI: 0.067–0.387,  $\beta = 0.831$ ;  $P = 0.010$ ). Baseline values of OPN predicted 3-year T2DM remission independently of body weight loss, lower BMI and duration of diabetes (OR: 1.046, 95% CI: 1.004–1.090;  $P = 0.033$ ).

**Conclusion.** – Although larger studies are still needed to confirm our preliminary results, pre-operative OPN serum levels might be useful for predicting 3-year T2DM remission independently of weight loss in patients undergoing bariatric surgery.

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### Introduction

Bariatric surgery is becoming a feasible therapy for patients with type 2 diabetes mellitus (T2DM) and obesity, and may eventually lead to diabetes remission. Interestingly, bariatric surgery has been shown to decrease blood glucose levels before weight reduction, suggesting a direct metabolic effect related to this surgical approach [1]. In this context, bariatric surgery may

also be referred to as ‘metabolic’ surgery. Randomized clinical trials have confirmed metabolic surgery as a highly effective strategy to improve glycaemic control, prevent microvascular and macrovascular complications, and even induce T2DM remission [2,3]. Furthermore, as metabolic surgery has become increasingly safer, this may strongly contribute to improving the cost-effectiveness of this surgical approach to diabetes compared with lifestyle and pharmacological interventions [4].

However, the biological modifications induced by metabolic surgery are much less clear. Alongside the well-known effects of weight loss on glucose homeostasis, body weight-independent

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**Abbreviations**

ADA	American diabetes association
AUC	area under the curve
BMI	body mass index
BPD	biliopancreatic diversion
CI	confidence interval
HOMA2	updated homoeostasis model assessment
HOMA2-%B	updated homoeostasis model assessment for $\beta$ -cell function
HOMA2-%S	updated homoeostasis model assessment for insulin sensitivity
IQR	interquartile range
OPN	osteopontin
ROC	receiver operating characteristic
RYGB	Roux-en-Y gastric bypass
SAT	subcutaneous adipose tissue
T2DM	type 2 diabetes mellitus
$\Delta$	delta (difference)

mechanisms are increasingly becoming of interest [5], although the relationship between post-surgical inflammatory decreases and metabolic improvement has yet to be clarified [6]. Even more elusive is the potential impact of pre-operative inflammatory status on clinical responses after metabolic surgery, especially as regards long-term outcomes.

For these reasons, our retrospective analysis of a previously published cohort aimed to assess whether baseline inflammatory status might have an impact on diabetes remission after metabolic surgery [7,8]. Of the different inflammatory molecules, our focus was on osteopontin (OPN), an emerging inflammatory biomarker closely linked to obesity and insulin resistance [9]. Thus, this was an investigation into the predictive role of pre-operative serum levels of OPN in cases of medium-term T2DM remission (3 years after surgery).

## Material and methods

### Patients, surgical procedures and follow-up

For this pilot observational retrospective analysis, 41 patients with T2DM undergoing bariatric surgery were enrolled from July 2007 to July 2009 at the Surgery Department of the Ospedale Policlinico San Martino in Genoa, Italy. After a multidisciplinary evaluation (including a psychologist, a psychiatrist, a diabetologist, a dietitian and a nurse), patients underwent either biliopancreatic diversion (BPD) or Roux-en-Y gastric bypass (RYGB), as described elsewhere [7,8]. Briefly, BPD was achieved by partial (two-thirds) distal gastrectomy and small-bowel transection 300 cm proximal to the ileocaecal valve. The distal stump was then anastomosed to the left corner of the gastric remnant, while the proximal stump was attached to the side of the distal ileum 50 cm proximal to the ileocaecal valve. The RYGB involved an antecolic Roux-en-Y reconstruction with a 100-cm biliopancreatic limb and a 250-cm alimentary limb. Immediately after a gastric pouch was created, gastroenterostomy was performed manually, with an end-to-side enteroenterostomy created using a 45-mm stapling device.

Patients were evaluated by the multidisciplinary team to determine their psychological and physical fitness for surgery. The assessment for surgery was individualized, based on the benefits

and peri- and post-operative risks for each candidate. The choice of surgical approach was also based on patients' behaviours and expectations, as BPD may be characterized by greater weight loss, but potentially more complications.

On the day prior to the bariatric surgery (baseline), serum samples were collected to test for haematological, biochemical and inflammatory profiles. Follow-up visits, including anthropometric measurements and serum collection, were performed at 1 and 3 years after the surgery. Among the entire cohort ( $n = 47$ ), three samples were missing and three patients were lost to follow-up, thereby leaving 41 patients available for analysis [10,11]. For these 41 patients, all serum samples were available and their follow-ups were complete.

The Ethics Committee of Ospedale Policlinico San Martino approved the protocol, which was performed in accordance with the guidelines of the Declaration of Helsinki. All patients also gave their written informed consent before entering the study.

### Study endpoint adjudication

The primary endpoint of the present study was to assess the predictive value of baseline serum levels of OPN for 3-year complete T2DM remission. According to the consensus definition provided by the American Diabetes Association, complete T2DM remission is defined as normal fasting glycaemia ( $< 5.6$  mmol/L) lasting for  $\geq 1$  year in the absence of any antidiabetic medication [12].

### HOMA2 indices

Updated computer models for homoeostasis model assessment (HOMA2; version 2.2.3 software for Windows from [www.dtu.ox.ac.uk](http://www.dtu.ox.ac.uk), accessed 1 January 2018) were used to calculate indices of insulin resistance (HOMA2-IR), beta-cell function (HOMA2-%B) and insulin sensitivity (HOMA2-%S). As the HOMA2-IR has not been validated in those treated with exogenous insulin [13], such patients were excluded from the assessment.

### Serum biomarker measurement

Serum levels of OPN were measured by colorimetric enzyme-linked immunosorbent assay (ELISA), as per the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). The limit of detection for OPN was 62.5 pg/mL, and the mean intra- and inter-assay coefficients of variation (CVs) were  $< 8\%$  [14,15].

### Statistical analysis

All analyses were performed with IBM SPSS Statistics for Windows version 23.0 software (IBM Corp., Armonk, NY, USA). Categorical data are presented as relative and absolute frequencies, while continuous variables are expressed as medians and interquartile range (IQR) as the normality assumption was not demonstrated. Differences from baseline to the 3-year follow-up are presented as delta ( $\Delta$ ). Intergroup comparisons were performed by Fisher's exact and Mann-Whitney  $U$ -tests, as deemed appropriate. Otherwise, comparisons between paired samples were made by Wilcoxon rank-sum test, and the data ranked. Linear relationships were determined by Spearman's correlation coefficient, whereas multiple linear regressions were performed to model baseline OPN values with HOMA2-%S. Multivariate logistic regression was also used to evaluate the prognostic ability of OPN to predict T2DM remission 3 years after bariatric surgery. Finally, post-hoc receiver operating characteristic (ROC) curve analyses, using MedCalc statistical software version 12.5.0.0 (MedCalc Software, Ostend, Belgium), were used to

estimate the predictive value of OPN, and the area under the curve (AUC) was calculated along with 95% confidence intervals (CIs). For all statistical analyses, a two-sided  $P < 0.05$  value was considered statistically significant.

## Results

### Three-year T2DM remission is weakly associated with clinical parameters at baseline

In patients who experienced T2DM remission (34.2%) 3 years after bariatric surgery, there remained a high prevalence of morbid obesity (57.1%) vs. 14.8% in those with no remission ( $P = 0.010$ ; Table 1). More specifically, median BMI Score was  $39.0 \text{ kg/m}^2$  (IQR: 32.2–45.1) compared with  $30.7 \text{ kg/m}^2$  (IQR: 28.6–33.1;  $P = 0.002$ ) in non-remitting patients. No other differences in gender, cardiovascular comorbidities, pharmacological therapies or type of bariatric surgery characterized patients with or without T2DM remission (Table 1). It is also noteworthy that circulating levels of OPN were significantly higher in patients who experienced T2DM remission vs no remission (50.97 ng/mL vs. 25.98 ng/mL, respectively;  $P = 0.009$ ; Table 1).

### Bariatric surgery was associated with clinical improvement in both study groups

During the 3-year follow-up, all patients experienced clinical improvement. Blood pressure (BP) fell in patients undergoing T2DM remission ( $P = 0.041$  and  $P = 0.027$  for systolic and diastolic BP, respectively) and, in particular, systolic BP was significantly lower in remission patients after 3 years ( $P = 0.020$ ; Fig. 1A, B). In addition, consistent with the high prevalence of morbid obesity in the T2DM remission group, these patients also had greater waist circumferences, body weight and body mass index (BMI) Scores at baseline ( $P = 0.003$ ,  $P = 0.024$  and  $P = 0.002$ , respectively; Fig. 1C, E). In all patients, even though bariatric surgery effectively reduced all three clinical parameters, patients who eventually had T2DM remission maintained bigger waist circumferences ( $P = 0.019$ ; Fig. 1C).

### Three-year T2DM remission is associated with improved lipid and glucose profiles

To identify the potential mechanisms associated with T2DM remission following bariatric surgery, an investigation of glucose

profiles over time was performed. Fasting glycaemia, insulinemia, and glycated haemoglobin (HbA<sub>1c</sub>) all improved during follow-up in both study groups (Fig. 2A–C). However, at the 1- and 3-year follow-ups, patients who achieved 3-year T2DM remission had lower levels of glycaemia and HbA<sub>1c</sub> compared with the non-remission group ( $P < 0.001$  for all; Fig. 2A, C). In addition, HOMA2-%B showed significantly improved beta-cell function from baseline to the 3-year follow-up only in the T2DM remission group ( $P = 0.043$ ; Fig. 2D), and was also better than in those without remission at the 1-year and 3-year follow-ups ( $P = 0.005$  and  $P = 0.001$ , respectively). In fact, both HOMA2-%S and HOMA2-IR were significantly improved from baseline over time in the T2DM remission group (Fig. 2E, F). Taken together, these results suggest that bariatric surgery is associated with a marked improvement of lipid and glucose profiles, particularly in patients who achieved 3-year T2DM remission.

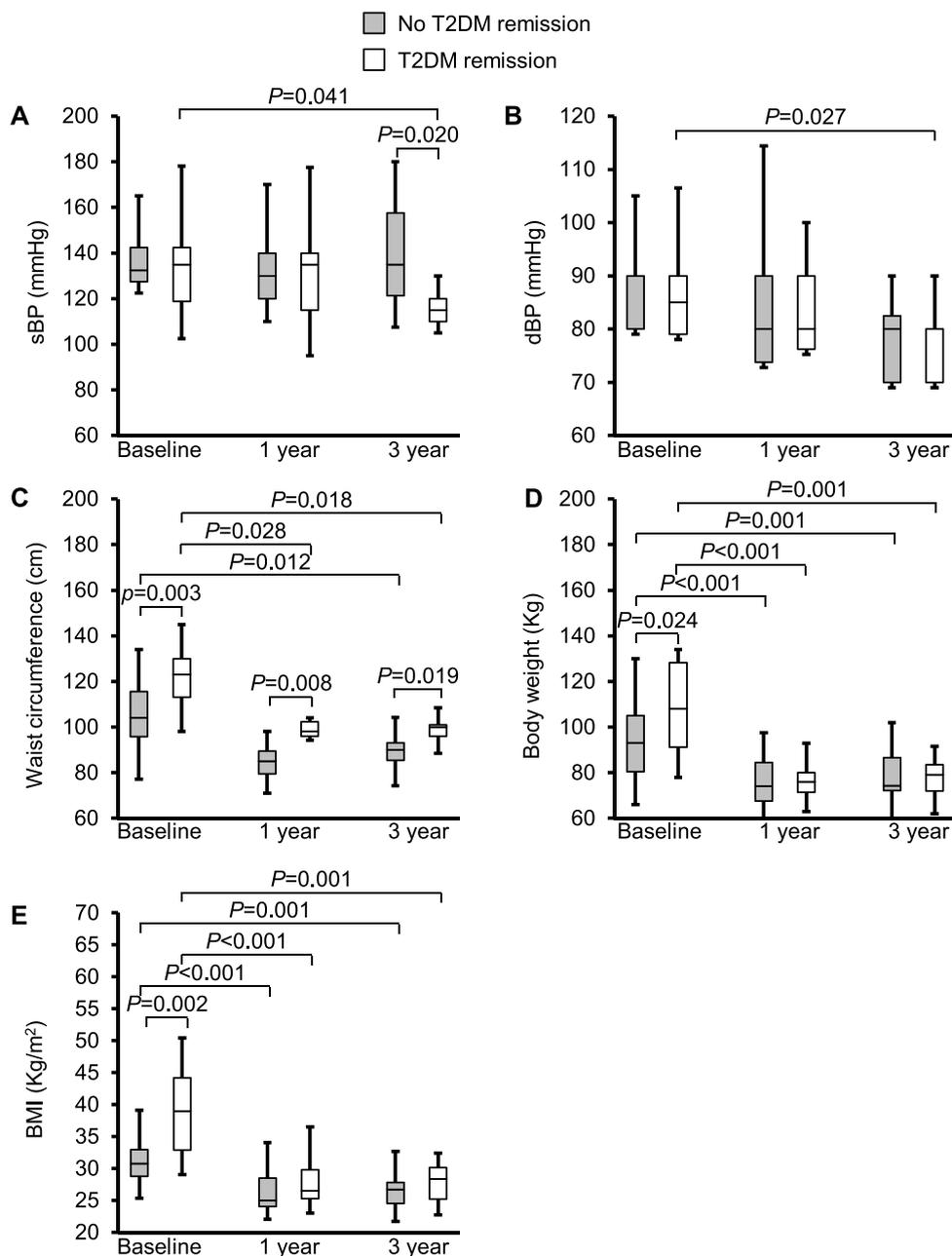
### Baseline OPN levels are associated with improved insulin resistance and independently predict 3-year T2DM remission

As reported above, baseline circulating OPN levels were significantly different in patients with vs. without 3-year T2DM remission (Table 1), thereby prompting an investigation into the potential correlation between OPN and changes ( $\Delta$ ) in clinical parameters over time:  $\Delta$  body weight ( $r = 0.445$ ,  $P = 0.006$ ) and  $\Delta$  BMI ( $r = 0.421$ ,  $P = 0.011$ ), but not  $\Delta$  waist circumference, correlated significantly with baseline OPN values (Table S1; see supplementary materials associated with this article online). As for insulin resistance, significant inverse relationships with baseline levels of OPN were found for  $\Delta$  HOMA2-%S ( $r = -0.614$ ,  $P = 0.015$ ) and for  $\Delta$  HOMA2-IR ( $r = 0.567$ ,  $P = 0.028$ ), but not for  $\Delta$  HOMA2-%B (Table S2; see supplementary materials associated with this article online). However, only HOMA2-%S at 3 years remained independently associated with baseline circulating levels of OPN on multivariate linear regression analysis (B: 0.227, 95% CI: 0.067–0.387,  $\beta = 0.831$ ;  $P = 0.010$ ; Table 2). Furthermore, baseline OPN values predicted T2DM remission independently of duration of diabetes,  $\Delta$  weight, and baseline values of BMI and fibrinogen [odds ratio (OR): 1.05, 95% CI: 1.01–1.10;  $P = 0.035$ ; Table 3], while ROC curve analysis confirmed that OPN had significant prognostic accuracy for predicting T2DM remission 3 years after bariatric surgery (AUC: 0.749, 95% CI: 0.589–0.870;  $P = 0.002$ ; Fig. S1; see supplementary materials associated with this article online). Using Youden's  $J$  statistic, serum OPN concentrations  $> 46.57 \text{ ng/mL}$  were identified as the best cut-off point, having a sensitivity of 70.37% and a specificity of 64.29%.

**Table 1**  
Characteristics of the two study groups with type 2 diabetes mellitus (T2DM) at baseline.

	Overall cohort (n = 41)	No 3-year T2DM remission (n = 27)	3-year T2DM remission (n = 14)	P
Age, years (IQR)	56 (49–61)	56 (51–61)	53.5 (42–62)	0.307
Men, n (%)	31 (75.6)	22 (81.5)	9 (64.3)	0.267
Body mass index, kg/m <sup>2</sup> (IQR)	31.8 (29.0–40.7)	30.7 (28.6–33.1)	39.0 (32.2–45.1)	<b>0.002</b>
Morbid obesity, n (%)	12 (27.3)	4 (14.8)	8 (57.1)	<b>0.010</b>
Hypertension, n (%)	21 (51.2)	13 (48.1)	8 (57.1)	0.744
Duration of diabetes, years (IQR)	12 (7–16)	12 (8–16)	10 (3–16)	0.734
Antidiabetic therapy:				0.380
Diet, n (%)	1 (2.4)	0 (0.0)	1 (7.1)	
Oral antidiabetic drug, n (%)	25 (61.0)	17 (63.0)	8 (57.1)	
Insulin, n (%)	15 (36.6)	10 (37.0)	5 (35.7)	
Bariatric surgery:				0.645
BPD, n (%)	35 (85.4)	22 (81.5)	13 (92.2)	
RYGB, n (%)	6 (14.6)	5 (18.5)	1 (7.1)	
BPD, n (%)	28.16 (19.93–53.08)	25.98 (17.60–44.47)	50.97 (26.49–79.31)	<b>0.009</b>

Data are expressed as medians (interquartile range, IQR) unless otherwise specified; between-group comparisons by Mann–Whitney  $U$ , Fisher's exact or Kruskal–Wallis tests as appropriate; BPD: biliopancreatic diversion; RYGB: Roux-en-Y gastric bypass; OPN: osteopontin.



**Fig. 1.** Changes in clinical characteristics during 3-year follow-up of bariatric surgery: patients with type 2 diabetes mellitus (T2DM) who experienced its remission showed significant decreases in (A) systolic (sBP) and (B) diastolic (dBp) blood pressure; (C) waist circumference, (D) body weight and (E) body mass index (BMI) also decreased in both study groups.

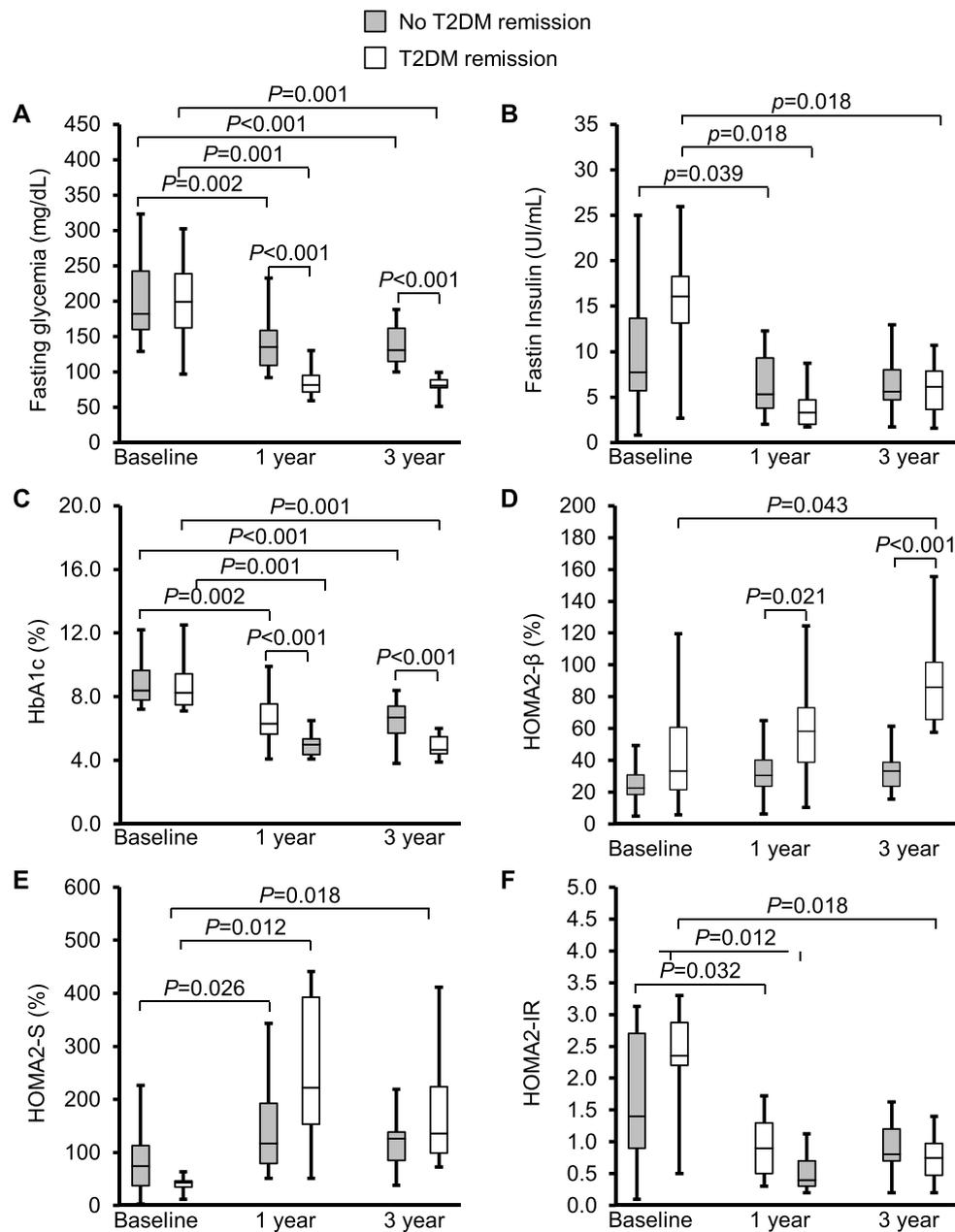
## Discussion

The first clinical finding of our study was the association between bariatric surgery and metabolic improvement as well as T2DM remission. As were recently reported, bariatric surgery can improve glucose profiles in T2DM through weight-loss-dependent and -independent mechanisms, along with later improvements in either inflammatory status or insulin resistance [5]. In fact, favourable changes in gastrointestinal hormones and bile acid signalling, alterations in gastrointestinal microbiota and modified intestinal nutrient-sensing mechanisms have also been associated with improved insulin sensitivity [16,17].

Although many of these mechanisms have only been demonstrated in animal models, compelling evidence is nevertheless

emerging in humans, with relevant clinical implications for maintaining T2DM remission over time [18]. The effectiveness of bariatric surgery for treating T2DM has been demonstrated especially in morbidly obese patients [3]. However, the present study could only partially confirm this observation, as there was a lack of differences in body weight and BMI reductions observed between our two study groups (T2DM remission vs. no T2DM remission) at the 1- and 3-year follow-ups.

These results suggest that qualitative rather than quantitative changes in body fat composition might be implicated in T2DM remission following bariatric surgery. However, potential glucose-lowering mechanisms independent of body weight loss may be hypothesized, and may provide a rationale to explain the similar benefits for obese and morbidly obese T2DM patients [19]. Indeed,



**Fig. 2.** Changes in glucose profiles and indices of insulin resistance during 3-year follow-up of bariatric surgery: (A) fasting glycaemia and (C) glycated haemoglobin (HbA<sub>1c</sub>) significantly improved in all patients after bariatric surgery, whereas (B) long-term reduction of serum insulin was limited to patients who experienced type 2 diabetes mellitus (T2DM) remission; (D) updated homoeostasis model assessment for beta-cell function (HOMA2-%β) increased only in the T2DM remission group, whereas (E) insulin sensitivity (HOMA2-%S) and (F) insulin resistance (HOMA2-IR) improved in both study groups, but was significant only in patients with T2DM remission.

**Table 2**

Multiple linear regression shows the independent association of osteopontin (OPN) with insulin sensitivity.

Baseline serum OPN (ng/mL)		β	P
Univariate			
3-year HOMA2-%S	0.196 (0.101–0.291)	0.738	< 0.001
Δ Body weight	1.107 (0.136–2.078)	0.450	0.027
Δ Body mass index	2.791 (0.20–5.562)	0.416	0.049
Multivariate			
3-year HOMA2-%S	0.227 (0.067–0.387)	0.831	0.010
Δ Body weight	−3.536 (−11.742–4.670)	−1.102	0.363
Δ Body mass index	9.725 (−11.030–30.480)	1.119	0.325

HOMA2-%S: updated homoeostasis model assessment for insulin sensitivity.

**Table 3**

Multiple logistic regression shows the ability of osteopontin (OPN) to predict type 2 diabetes mellitus (T2DM) remission during follow-up.

3-year T2DM remission	OR (95 % CI)	P	OR (95% CI)	P	OR (95% CI)	P
Baseline serum OPN	1.04 (1.001–1.09)	<b>0.036</b>	1.04 (1.001–1.09)	<b>0.041</b>	1.05 (1.01–1.10)	<b>0.035</b>
Duration of diabetes	0.92 (0.77–1.09)	0.316	0.91 (0.77–1.09)	0.312	0.91 (0.75–1.09)	0.906
Δ Body weight	1.08 (1.01–1.17)	<b>0.041</b>	1.09 (0.95–1.26)	0.203	1.12 (0.95–1.31)	0.169
Baseline body mass index			0.98 (0.77–1.25)	0.856	0.95 (0.71–1.27)	0.716
Fibrinogen					0.99 (0.981–1.01)	0.692

OR: odds ratio; CI: confidence interval.

new qualitative concepts of different types of ‘obesities’ (such as metabolically healthy obese and unhealthy obese patients) instead of ‘obesity’ could lead to consideration of BMI and body weight as variables that only partially contribute to T2DM. Also, the benefits induced by metabolic surgery suggest that additional inflammatory and metabolic mediators could actively influence clinical outcomes such as 3-year T2DM remission [20]. Thus, this raises another pathophysiological issue with the bariatric-surgery-induced changes in inflammation and insulin resistance seen in patients with 3-year T2DM remission.

Nevertheless, the beneficial effects of metabolic surgery on systemic inflammation independent of body weight loss in patients with T2DM remission continue to be controversial. Some studies have traditionally described low-grade systemic inflammation (mainly assessed by C-reactive protein) as a negative predictor of response to bariatric surgery [21,22]. On the other hand, contrasting results have also been reported [10,23].

In the present study, it was observed that pre-operative serum levels of OPN predicted 3-year T2DM remission independently of duration of diabetes, baseline values of BMI and fibrinogen, and post-operative weight loss as well. In addition, there are still some concerns over the potential role of antidiabetic therapy prior to surgery, as it is likely that different therapeutic needs might influence post-surgical clinical outcomes through perhaps a preexistent resistance to treatment or because of the pleiotropic effects of some antidiabetic drug classes. Furthermore, although a recent study reported a significant difference between insulin-dependent vs. non-insulin-dependent diabetes patients [24], further studies are still warranted. Moreover, in our cohort, baseline serum levels of OPN correlated positively with weight loss and lower BMIs, and even more strongly with post-surgical recovery of insulin sensitivity.

Recently, Garrido-Sánchez and colleagues [25] hypothesized that bariatric surgery might be especially useful for patients with higher levels of inflammatory markers due to the differential role of visceral vs. subcutaneous adipose tissue (SAT). In their study, patients experiencing T2DM remission after bariatric surgery were characterized by having the highest pre-operative levels of inflammatory messenger RNA (mRNA) gene expression in SAT. More specifically, mRNA upregulation involved the expression of macrophage markers CD11b, CD163 and CD11c. Indeed, it is certainly intriguing that the increased expression of OPN and its receptor CD44 in SAT is closely associated with macrophage accumulation rather than localized production within SAT [26,27]. In addition, various studies have described OPN as a promoter of pro-inflammatory macrophage polarization and insulin resistance [28–30].

Finally, our study did not analyze post-surgical changes in serum OPN levels, as they have been generally described to increase with no correlation to lower body weight/BMI or insulin sensitivity [31,32]. Therefore, our findings suggest that baseline high serum OPN may be particularly useful for identifying those T2DM patients who are likely to derive more benefit (3-year disease remission) with bariatric surgery. However, it is acknowledged that any hypothesis of a direct protective or deleterious role of OPN in T2DM after bariatric surgery is highly speculative, as high OPN levels in T2DM

patients could be reflecting more baseline inflammation, which actively increases insulin resistance, or merely an innocent ‘bystander’ biomarker.

Therein lies the main limitation of our present study. Yet, the growing body of evidence in this field should prompt further researches to clarify the impact of pre-operative inflammatory status on insulin resistance and clinical responses to bariatric surgery. Likewise, the small sample size and single-centre design of the present cohort should also be considered a further limitation to generalization of our results. Moreover, the number of patients who underwent RYGB was very small, making it impossible to properly analyze this surgical approach as a potential determinant of clinical outcome [33]. Finally, it was possible to evaluate only medium-term T2DM remission (3 years after bariatric surgery), whereas T2DM remission more frequently arises > 5 years after surgery [33], which means that long-term relapses now deserve future investigations.

## Conclusion

High pre-operative OPN serum levels can predict 3-year T2DM remission, and correlate positively with lower post-operative weight/BMI and recovery of insulin sensitivity. These findings may also contribute towards identifying inflammatory status as a crucial determinant of T2DM remission after bariatric surgery. Thus, large-scale multicentre studies are now warranted to establish whether OPN (alone or in a panel with other inflammatory biomarkers) can identify the population most likely to derive the most benefit from bariatric surgery.

## Disclosure of interest

The authors declare that they have no competing interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.diabet.2018.09.007>.

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