

Improvement in the cardiovascular profile of patients with morbid obesity following bariatric surgery

Effect on hypercoagulability

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Abstract

Obesity is an inflammatory state related to vascular endothelium dysfunction. It generates a biological situation of hypercoagulability increasing the risk of thrombosis. This prothrombotic condition could be improved by bariatric surgery.

The main objective was to analyze the impact of bariatric surgery on cardiovascular risk factors (CVRF) associated with changes in thrombin generation and procoagulant activity of microparticles (MP).

We present a prospective longitudinal study including consecutive patients candidate for bariatric surgery. We performed 3 sequential clinical visits: at inclusion, before surgery after completing the modified fasting phase, and 6 months after surgery. We analyzed CVRF, thrombin generation, and MP activity. The data analysis was performed using a logistic regression model to determine changes over time of hemostatic parameters and body mass index (BMI). McNemar test for binary variables was used to analyze the CVRF.

We included 94 patients (66 women), with an average age of 45.7 ± 10.1 years. The mean BMI reduction at the end of the follow-up was 15.5 ± 4.2 kg/m². We detected a statistically significant improvement in CVRF: hypertension, diabetes mellitus, dyslipidemia, and obstructive sleep apnea, as well as a significant reduction in thrombin generation capacity and procoagulant MP activity.

Massive weight loss induced by bariatric surgery improves the cardiovascular profile, associated with a reduction in the hypercoagulable status.

Abbreviations: ACCP = American College of Chest Physicians, BMI = body mass index, CVRF = cardiovascular risk factors, DLP = dyslipidemia, DM = diabetes mellitus, ETP = endogenous thrombin potential, LMWH = low-molecular-weight heparin, LT = lag time, MP = microparticles, OSA = obstructive sleep apnea, PAI-1 = plasminogen activator inhibitor type 1, PE = pulmonary embolism, PPP = platelet-poor plasma, ST = start tail, TAFI = thrombin-activatable fibrinolysis inhibitor, TF = tissue factor, TGT = thrombin generation test, TTP = time to peak, VT = venous thrombosis.

Keywords: bariatric surgery, microparticles, obesity, thrombin generation, thrombosis

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1. Introduction

Obesity is characterized by a state of hypercoagulability resulting from changes in the hemostatic profile and fibrinolytic activity.^[1,2] In addition, obesity is considered a chronic systemic inflammatory disease, as evidenced by the increase of pro-inflammatory cytokines and acute phase reagent proteins.^[3]

Inflammation induces a dysfunction of the vascular endothelium, with an overexpression of tissue factor (TF), a protein which is the main activator of the hemostatic system.^[3,4]

This state of hypercoagulability occurs through Factor X activation that increases thrombin generation.^[5] In addition, endothelial injury causes a decrease in fibrinolytic capacity, by overproduction of endothelial inhibitors of plasminogen activator inhibitor type 1 (PAI-1) as well as through an increase in thrombin-activatable fibrinolysis inhibitor (TAFI).^[6] This prothrombotic state contributes to an increased risk of venous thrombosis (VT) and cardiovascular ischemic diseases.^[4,7]

Furthermore, circulating procoagulant microparticles (MP) which are small vesicles rich in anionic phospholipids and TF found in endothelial cells, platelets, and leukocytes, are also increased in patients with cardiovascular clinical risk factors (CVRF).^[8,9]

The procoagulant activity of MP is related to their high ability to join TF boosting thrombin formation.^[10,11] Increased levels of

different MP subpopulations are associated with metabolic syndrome and oxidative stress.^[12]

An association has been established between obesity and type 2 diabetes mellitus (DM) or insulin resistance, hypertension, and dyslipidemia (DLP), contributing to an increased risk of cardiovascular diseases development.^[13,14]

Bariatric surgery-induced weight loss is a good model for investigating the effects of reducing body weight and modifying CVRF.^[2]

In addition, patients undergoing bariatric surgery have a high risk of developing postoperative deep VT and/or pulmonary thromboembolism (PE), which are the major cause of morbidity and mortality in these patients. The overall incidence of deep VT fluctuates between 1% and 3%, PE between 0.1% and 1.13%, while fatal PE, although rare, is 0.23%, despite administration of antithrombotic prophylaxis.^[15,16]

However, obese patients undergoing bariatric surgery present a significant decrease in thrombin generation, demonstrating the beneficial effect on cardiovascular risk.^[4,10,17–20] Less information is available about changes in MP concentration and their association with weight loss and bariatric surgery.

Considering that bariatric surgery could ameliorate the cardiovascular profile, we hypothesized that prothrombotic markers could decrease significantly as CVRF improve.

The objective of our study was to analyze the impact of bariatric surgery on the reduction of CVRF and its association with changes in thrombin generation and procoagulant activity of MP.

2. Patients and methods

2.1. Study design

This is a prospective longitudinal study including consecutive patients over 18 years of age, candidate for bariatric surgery in our hospital.

The sample size was defined a posteriori. The objective was to compare the mean body mass index (BMI) at inclusion and after surgery. With this objective and a sample size of 94 patients, we obtained a power close to 100%.

2.2. Inclusion criteria

Morbid obese patients over 18 years of age, candidate for bariatric surgery were included if the BMI was above 40 kg/m² or BMI was above 35 kg/m² and with at least one of the following comorbidities: DM, hypertension, DLP, or obstructive sleep apnea (OSA). Informed consent was obtained prior to participation in the study.

2.3. Exclusion criteria

Patients under anticoagulant or antiplatelet treatment at the time of inclusion were excluded. We also excluded patients with previous history of arterial or venous thrombosis as well as those with disorders concerning hemostasis: liver disease, active inflammatory process, pregnancy, postpartum, oral contraceptive intake, hormone replacement treatment, or cancer history.

In our study 2 types of bariatric surgery were performed depending on each patient's individual situation and surgeon's preferences: Roux-en-Y gastric bypass: a small sac is created from the stomach and connected to the small intestine, tubular gastrectomy: reduces about 80% of the stomach.

The study was conducted in accordance with the basic principles of the World Medical Association Declaration of Helsinki and complied with the standards described in the European Union Guidelines for good clinical practice. This study was approved by the local ethics committee.

All patients received postoperative thromboprophylaxis following the recommendations of the American College of Chest Physicians (ACCP) guidelines for moderate-high thrombotic risk surgical patients.^[21]

2.4. Sample collection

Blood samples were obtained in 8-hour fasting by puncture of an antecubital vein and anticoagulated with 0.129 M sodium citrate (1:9 ratio). Three medical visits including blood sample collection were scheduled in this study: at inclusion, once the modified fasting phase was completed just before surgery, and 6 months after surgery.

*The modified fasting phase is based on a presurgery diet designed for losing 10% of excess body weight. The goal of this fasting phase is to prepare the patient safely for the operation and recovery and to achieve better eating habits. A 3-week diet of 1200 calories per day is established for women and 1500 calories per day for men.

Platelet-poor plasma (PPP) was immediately obtained by double centrifugation at 2500 × g for 15 minutes at 22°C. The aliquots were stored at –80°C until processing. Samples were defrosted at 37°C for 10 minutes prior to analysis.

In case of VT development, the patient was excluded from the study.

2.5. Clinical variables

The classic CVRF were evaluated at inclusion and at the end of the study. We considered CVRF remission when drug treatments were no longer required for their control, nor non-invasive ventilation in the case of OSA. Hematological parameters and BMI were evaluated in all 3 medical visits.

Every thrombotic or hemorrhagic event, including severity, location, treatment, and dose was recorded in the database.

3. Hematological parameters

3.1. Determination of thrombin generation

3.1.1. Thrombin generation test (TGT). The fluorometric method described by Hemker et al^[22] was used. Thrombin generation was analyzed using the calibrated automatic thrombogram (CAT, Diagnostica Stago, Paris, France). TGT provides information on the start time of thrombin generation (lag time, LT minutes), the endogenous thrombin potential or total amount of thrombin generated (ETP, nMol/L min), the peak of thrombin concentration (nMol/L), the time to reach the maximum peak of thrombin (TTP, minutes), and the time to thrombin neutralization (start tail, ST, minutes). Normal values are not defined in the literature as this technique is not standardized yet. Its clinical usefulness is related to the evolutionary values obtained in the scheduled blood tests throughout the study.

3.2. Determination of the procoagulant functional activity of MP

We used the coagulative technique (STA procoagulant PPL, Diagnostica Stago, Paris, France) in PPP in automatic coagul-

ometer (STA-Rac, Diagnostica Stago, Paris, France). We measured the coagulation time in the presence of calcium and a phospholipid-free substrate.^[23] A shortening in clotting time compared with normal values provided by the manufacturer means an increase in procoagulant phospholipid activity. Although these values may vary depending on local preanalytical conditions, the manufacturer described 72 ± 5.6 seconds as the normal range.^[24]

3.3. D-dimer

The D-dimer was performed using the immunoprecipitation technique (D-dimer, Diagnostica Stago, Paris, France) in PPP, by a monoclonal antibody in automatic coagulometer (STA-Rac, Diagnostica Stago, Paris, France). Normal range was $<0.5 \mu\text{g/mL}$.

3.4. Statistical analysis

Qualitative variables were described as absolute and relative frequencies, and quantitative variables as mean and standard deviation or median and interquartile range, as appropriate. The McNemar test was used to evaluate the effect of intervention in binary variables. We estimated a logistic regression model to determine changes over time in hematological parameters and BMI. The correlation analysis between 2 quantitative variables was performed using the Pearson coefficient if both variables followed a normal distribution or the Spearman test if at least 1 of the variables did not have a normal distribution. Statistical significance was set at 5%. The statistical software used was IBM SPSS version 20 (Chicago, IL).

4. Results

4.1. Patient characteristics

Ninety-four patients were included in the analysis. The clinical characteristics of the patients at inclusion are summarized in Table 1.

Regarding the type of bariatric surgery, a Roux-en-Y gastric bypass was performed in 61 patients (65%), while a tubular gastrectomy was carried out in 33 patients (35%).

4.2. BMI evaluation

A statistically significant reduction in BMI throughout the medical visits scheduled for this study has been objectified. A BMI of $49.6 \pm 7.3 \text{ kg/m}^2$ was observed at inclusion, $44.1 \pm 7.4 \text{ kg/m}^2$ prior to surgery, and $34.1 \pm 6.7 \text{ kg/m}^2$ 6 months after surgery, amounting to an average reduction of $15.5 \pm 4.2 \text{ kg/m}^2$ (Fig. 1).

Table 1

Patients' characteristics at inclusion.

Total: 94 patients	
Women, n (%)	66 (72.5)
BMI (kg/m^2 , mean \pm SD)	49.6 ± 7.3
Age (y, mean \pm SD)	45.7 ± 10.1
Diabetes mellitus, n (%)	31 (34.1)
Hypertension, n (%)	40 (44)
Dyslipidemia, n (%)	28 (30.8)
Obstructive sleep apnea, n (%)	59 (64.8)

BMI=body mass index, SD=standard deviation.

4.3. Thrombin generation evaluation

We found a statistically significant sequential reduction in ETP, as well as in the maximum peak of thrombin concentration. This was most evident following bariatric surgery. Similarly, a statistically significant improvement in the time to reach the peak of thrombin and ST was observed. However, the differences in LT along the visits were not significant statistically (Fig. 2). In addition, we found a positive correlation with statistical significance between total BMI reduction and the improvement in the main thrombin generation parameters ($r=0.5$ and $P < .001$ for ETP and BMI reduction and $r=0.43$ and $P < .001$ for maximum peak of thrombin and BMI reduction).

4.4. MP procoagulant activity evaluation

We found a statistically significant reduction in the activity of procoagulant MP throughout the consecutive medical visits. Thus, at inclusion we obtained a coagulation time in seconds of 47.8 ± 19.3 that increased to 76.4 ± 18.6 seconds at the end of the study (Fig. 3).

4.5. D-dimer

Although d-dimer remained within the normal range established by the manufacturer, we found a statistically significant difference in d-dimer at inclusion and before surgery (Fig. 4).

Regarding CVRF evolution, we observed a clinical improvement with statistical significance (Table 2).

We compared hematological parameters (thrombin generation and MP) and clinical variables (CVRF and BMI) depending on the type of surgery. We found that patients undergoing Roux-en-Y gastric bypass had a significant higher BMI reduction and hypertension correction and less endogenous thrombin potential than patients undergoing tubular gastrectomy (Table 3).

Finally, we evaluated changes in previous hematological parameters (thrombin generation and MP) in relation to the presence of the main CVRF (hypertension, DM, DLP, and OSA) 6 months following the intervention, considering only those patients with every CVRF at inclusion (Tables 4–7).

We only detected a venous splenic thrombosis 15 days after intervention, probably associated with the surgical procedure (a tubular gastrectomy was performed). This patient was excluded from the study. No other thrombotic events were observed during follow-up. There was no clinically significant bleeding and only localized bruising was found at the injection site of low-molecular-weight heparin (LMWH) in 40% of patients.

5. Discussion

This prospective study illustrates the benefits of bariatric surgery-induced massive weight loss in prothrombotic status in a broad cohort of patients studied at our institution. Although some studies in bariatric surgery settings studying thrombotic biomarkers have been published,^[2,9,15–20,25–29] our study includes the largest sample size recruited in a single center evaluating both thrombin generation and MP activity. In addition, to the best of our knowledge, we have not found any publication including an analysis once completing the modified fasting phase prior to bariatric surgery. Thereaux and Stolberg conducted a presurgery examination. However, they do not indicate whether the sample was obtained following the modified fasting phase.^[18–20]

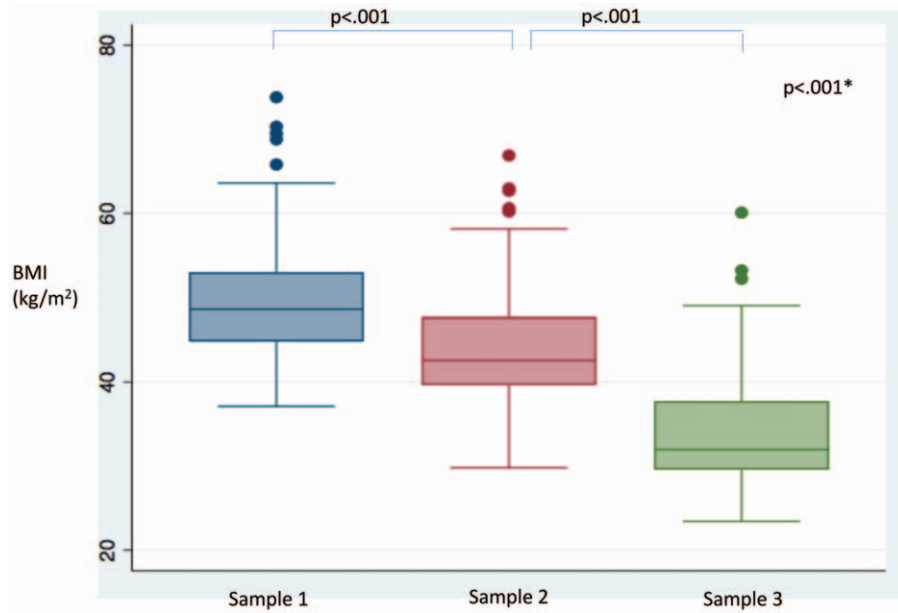


Figure 1. Variation of body mass index (BMI) during the intervention. *P* values between each visit are described. *P* value* indicates the value between the first and third visit.

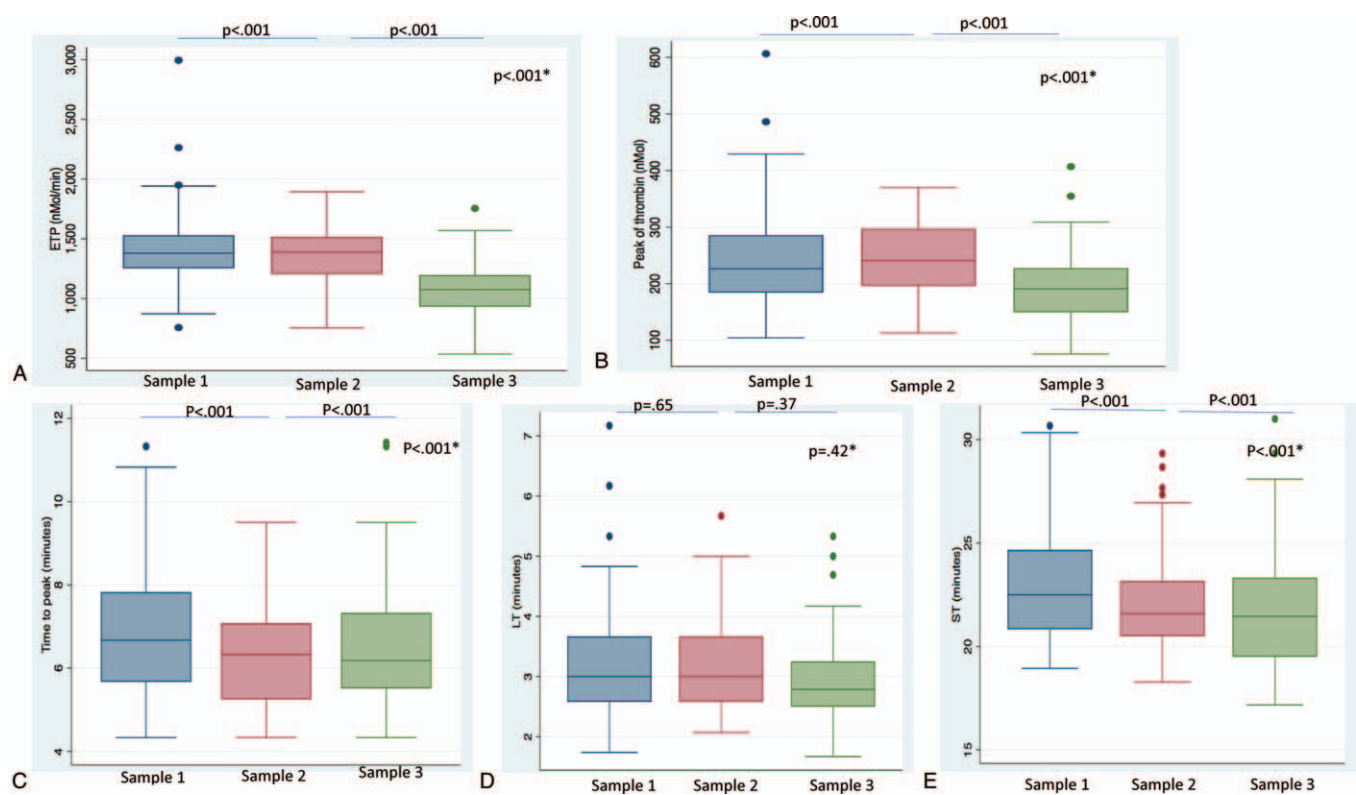


Figure 2. Changes in thrombin generation parameters along the medical visits. (A): Variation of endogenous thrombin potential during the intervention (ETP, nMol/L min). (B): Variation of mean thrombin peak during the intervention (nMol/L). (C): Variation of time to reach the peak of thrombin during the intervention (TTP, minutes). (D): Variation of lag time during the intervention (LT, minutes). (E): Variation of start tail during the intervention (ST, minutes). *P* values between each visit are described. *P* value* indicates the value between the first and third visit. ETP=endogenous thrombin potential, LT=lag time, ST=start tail, TTP=time to peak.

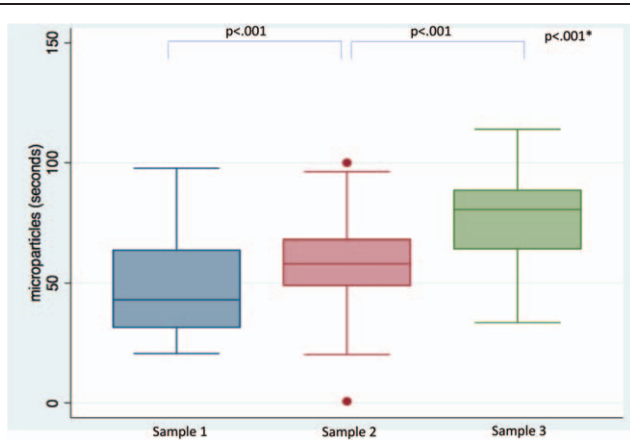


Figure 3. Variation of microparticles during the intervention (MP, seconds). *P* values between each visit are described. *P* value* indicates the value between the first and third visit. MP=microparticles.

In our study, according to the ACCP guideline recommendations, all patients received thromboprophylaxis with LMWH for 30 days after the operation. Some studies reported a 1-month appointment after bariatric surgery.^[18–20,26] However, to avoid any confounding factor induced by thromboprophylaxis, we decided not to evaluate clinical and hemostatic data when the patient was on LMWH, as LMWH could interfere with thrombin generation and procoagulant MP activity.

We observed an average BMI reduction of $15.5 \pm 4.2 \text{ kg/m}^2$ from inclusion to the last visit (6 months after surgery), similar to the series described in the literature.^[17,27–29]

Our study, with 94 patients included, is the largest in number of patients including thrombin generation in a bariatric surgery setting in a single institution. In our population, a statistically significant improvement in thrombin generation was associated with a progressive reduction in BMI (Fig. 2). This improvement was already evident once the modified fasting phase was completed and reinforced throughout the postoperative period. Additionally, we found a positive correlation with statistical

Table 2

Changes in cardiovascular risk factors after bariatric surgery.

	At inclusion n (%)	Six months following surgery n (%)	<i>P</i> value
Hypertension	40 (44)	22 (24.2)	<i>P</i> < .001
Diabetes mellitus	31 (34.1)	11 (12.1)	<i>P</i> < .001
Dyslipidemia	28 (30.8)	11 (12.1)	<i>P</i> < .001
Obstructive sleep apnea	59 (64.8)	43 (47.3)	<i>P</i> = .003

significance between the total BMI reduction and the main thrombin generation parameters (i.e., ETP and maximum peak of thrombin concentration).

Our results are consistent with those published by Ay et al,^[2] although some differences were found. This group included 36 obese patients with an average BMI of $45 \pm 5 \text{ kg/m}^2$ evaluated before and 2 years after surgery. However, the average BMI of our series at inclusion was $49.6 \pm 7.3 \text{ kg/m}^2$ with a follow-up period of 6 months.

Regarding thrombin generation, we used the fluorometric method designed by Hemker et al.^[22] However, Ay et al^[2] used the technothrombin generation assay. There are discrepancies in the results that could be related to TF concentration and the trigger reagent (TF), which can modify the sensitivity and specificity of the test. In our study, we suggested an intermediate TF concentration (3pM) to avoid the drawbacks of extreme concentrations.

We use the semiautomated fluorogenic method designed by Hemker, as it is the most reported in literature.^[30] In addition, this method showed that the coefficient of variation of ETP for each individual was around 8% (7.4 extremes 6–11) and the interindividual variability was 17.5%.^[27] Other authors like Thereaux and Stolberg also used the fluorogenic method designed by Hemker et al.^[22] The differences in raw data comparing these studies with ours could also be related to the TF concentration (1 and 5 pM respectively as opposed to 3pM in our study).^[18–20]

Regarding MP, we observed a decrease in their procoagulant activity throughout the scheduled medical appointments. We

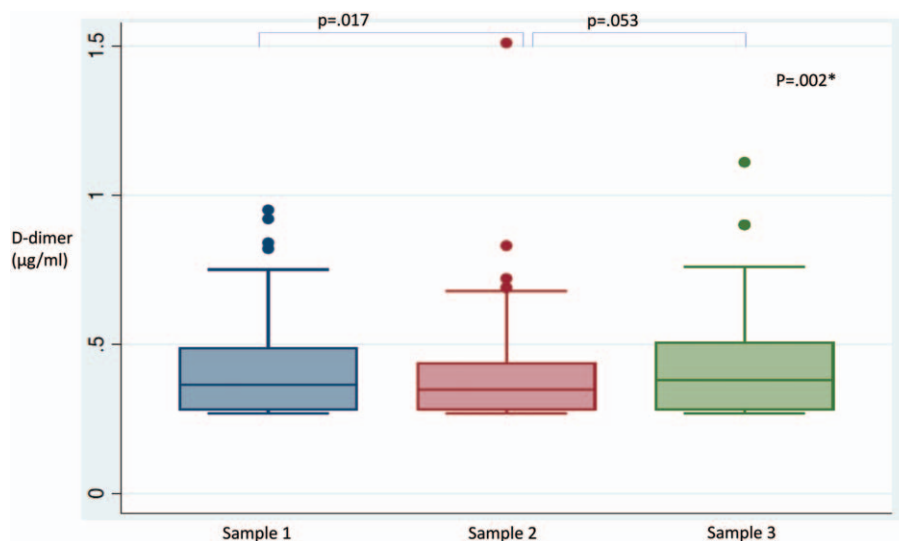


Figure 4. Variation of d-dimer during the intervention. *P* values between each visit are described. *P* value* indicates the value between the first and third visit.

Table 3
Hematological and clinical variables changes depending on type of surgery.

	Roux-en-Y gastric bypass (n = 58)	Tubular gastrectomy (n = 31)	P value
BMI, kg/m ²	30.80 (28.76–32.81)	39.29 (35.07–42.96)	<.001
ETP, nMol/L min	1036.73 (928.31–1141.1)	1126.32 (1030.39–1245.88)	.029
Thrombin peak, nMol/L	184.25 (149.85–223.45)	199.61 (141–247.43)	.17
TTP, min	6.17 (5.33–7.09)	6.58 (5.52–7.67)	.21
LT, min	2.67 (2.4–3.06)	3 (2.52–3.67)	.023
ST, min	21.2 (19.5–23.2)	22.16 (20.06–24.67)	.22
MP, s	78.3 (63.2–86.4)	85.3 (66.5–90.5)	.35
Hypertension	8 (13.7)	13 (42)	.002
DM	6 (10.34)	3 (9.6)	.92
DLP	5 (8.62)	6 (19.3)	.14
OSA	24 (41.37)	18 (58)	.13

Quantitative values expressed as median (percentil25–percentil75).

Qualitative values expressed as absolute frequency (percentage).

BMI = body mass index, DLP = dyslipidemia, DM = diabetes mellitus, ETP = endogenous thrombin potential (nMol/L min), LT = lag time (minutes), MP = microparticles (seconds), OSA = obstructive sleep apnea, ST = start tail (minutes), TTP = time to reach the maximum thrombin peak (TTP, minutes).

determined the MP activity using the coagulative technique instead of flow cytometry.^[8] Campello et al^[9] measured the MP using not only flow cytometry but also the coagulative assay, since this activity linearly correlates with the functional activity of MP in the sample. Our group demonstrated that the coagulative assay measuring coagulation time in a system dependent on the procoagulant phospholipid content of the sample is feasible, cheaper and is, therefore, a valid option for studying MP activity.^[31] Other groups such as Cheng et al^[26] and Stepanian et al^[25] achieved similar results 12 months after surgery using flow cytometry. However, flow cytometry might not detect all MP sizes, as they could be below the detection method threshold. For this reason, we decided to introduce the test that measures the overall procoagulant activity of MP instead of using flow cytometry.

An improvement in metabolic and inflammatory parameters after surgery was correlated with a decrease in procoagulant MP activity and a massive weight loss.^[2,3,9,14,25] In our study, cardiovascular risk in obese patients is clearly reduced after bariatric surgery, mainly hypertension, DM, and DLP.

Nevertheless, when we compared changes in thrombin generation parameters and procoagulant MP activity associated with every CVRF 6 months following bariatric surgery, we did not observe statistical differences.

Therefore, according to our results, an improvement in hypercoagulability parameters is mainly due to weight loss

induced by presurgery diet followed by bariatric surgery, but not to changes in the CVRF.

D-dimer was normal at inclusion. The exclusion of patients with arterial or venous thrombosis and other inflammatory diseases that could affect d-dimer and the clinical stability of the patient could explain this result. D-dimer remained within normality 6 months after the surgery due to the improvement in the hypercoagulability parameters and the antithrombotic effect promoted by weight loss.

When evaluating changes in hypercoagulability parameters and clinical variables (CVRF and BMI) depending on the type of surgery, patients undergoing Roux-en-Y gastric bypass had a higher BMI reduction and hypertension correction and less endogenous thrombin potential with statistical significance than patients undergoing tubular gastrectomy. Although other parameters did not reach the statistical significance, massive weight loss is more evident with Roux-en-Y gastric bypass and enhances the improvement in the hypercoagulable state and comorbidities.

The main strength of our study is that it is based on a prospective follow-up of a broad cohort of consecutive patients candidate for bariatric surgery in a single reference center. In addition, we included an evaluation of the effect of the modified fasting phase and its effect on the state of hypercoagulability before surgery.

Table 4
Changes in hematological parameters 6 months following surgery depending on the presence of hypertension.

	No hypertension (n = 19)	Hypertension (n = 21)	P value
ETP, nMol/L min	1038 (929–1234)	1093 (928–1150)	.426
Thrombin peak, nMol/L	176 (150–204)	197 (152–229)	.426
TTP, min	6 (5–7)	6 (5–7)	.520
LT, min	3 (2–4)	3 (2–4)	.460
ST, min	22 (21–23)	21 (19–23)	.368
MP, s	74 (62–89)	73 (63–86)	.516

Changes were assessed in patients with hypertension at inclusion (n = 40). Values expressed as median (percentil25–percentil75).

ETP = endogenous thrombin potential (nMol/L min), LT = lag time (minutes), MP = microparticles (seconds), ST = start tail (minutes), TTP = time to reach the maximum thrombin peak (TTP, minutes).

Table 5
Changes in hematological parameters 6 months following surgery depending on the presence of DM.

	No DM (n = 21)	DM (n = 9)	P value
ETP, nMol/L min	1075 (1011–1136)	1073 (987–1163)	.414
Thrombin peak, nMol/L	199 (176–229)	182 (180–209)	.414
TTP, min	6 (5–8)	6 (6–8)	.410
LT, min	3 (2–4)	3 (2–4)	.740
ST, min	21 (19–23)	21 (20–23)	.613
MP, s	74 (64–85)	79 (62–91)	.506

Changes were assessed in patients with DM at inclusion (n = 30). Values expressed as median (percentil25–percentil75).

DM = diabetes mellitus, ETP = endogenous thrombin potential (nMol/L min), LT = lag time (minutes), MP = microparticles (seconds), ST = start tail (minutes), TTP = time to reach the maximum thrombin peak (TTP, minutes).

Table 6
Changes in hematological parameters 6 months following surgery depending on the presence of DLP.

	No DLP (n=19)	DLP (n=9)	P value
ETP, nMol/L min	1042 (927–1136)	1025 (928–1163)	.409
Thrombin peak, nMol/L	175 (148–193)	200 (193–252)	.409
TTP, min	6 (5–8)	6 (5–7)	.211
LT, min	3 (2–4)	3 (2–4)	.209
ST, min	21 (20–23)	19 (18–2)	.554
MP, s	63 (56–74)	78 (69–88)	.476

Changes were assessed in patients with DLP at inclusion (n=28). Values expressed as median (percentil25–percentil75).

DLP=dyslipidemia, ETP=endogenous thrombin potential (nMol/L min), LT=lag time (minutes), MP=microparticles (seconds), ST=start tail (minutes), TTP=time to reach the maximum thrombin peak (TTP, minutes).

Table 7
Changes in hematological parameters 6 months following surgery depending on the presence of OSA.

	No OSA (n=20)	OSA (n=38)	P value
ETP, nMol/L min	1094 (1012–1272)	1052 (923–1159)	.438
Thrombin peak, nMol/L	205 (150–245)	189 (153–226)	.438
TTP, min	6 (5–7)	6 (5–7)	.549
LT, min	3 (2–4)	3 (2–4)	.186
ST, min	21 (20–23)	21 (19–23)	.424
MP, s	84 (65–91)	75 (63–88)	.406

Changes were assessed in patients with OSA at inclusion (n=58). Values expressed as median (percentil25–percentil75).

ETP=endogenous thrombin potential (nMol/L min), LT=lag time (minutes), MP=microparticles (seconds), OSA=obstructive sleep apnea, ST=start tail (minutes), TTP=time to reach the maximum thrombin peak (TTP, minutes).

We have avoided possible confusion factors by excluding patients with hypercoagulable states (see exclusion criteria) and those being treated with anticoagulants or antiplatelet treatments.

The main limitation of our study was the absence of a control group. However, every patient was considered his/her own control, so we were able to analyze the effects on hemostatic parameters and CVRF throughout the different medical visits.

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Investigation: Ana Marco.

Methodology: Pascual Marco.

Supervision: Pascual Marco.

Validation: Ana Marco.

Writing – original draft: Ana Marco.

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