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Prospective assessment of fibrinolysis in morbid obesity: tissue plasminogen activator resistance improves after bariatric surgery

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Abstract

Background: Morbid obesity is associated with an increased risk of thrombotic events, which has been attributed to increased thrombotic activity. Multiple mechanisms have been proposed to explain this increased risk, including an inflammatory state with upregulation of procoagulant and antifibrinolytic proteins. We therefore hypothesize that patients with morbid obesity are hypercoagulable and will revert to normal after bariatric surgery.

Objectives: To evaluate changes in the hypercoagulable state after bariatric surgery.

Setting: University Hospital, Bariatric Center of Excellence, United States.

Methods: Thromboelastography (TEG) data were collected on 72 subjects with morbid obesity, with 36 who had 6 months of follow-up after bariatric surgery. TEG data of 75 healthy subjects (HS) without obesity, recent trauma or surgery, acute infection, or chronic conditions (e.g., liver, cardiovascular, or kidney disease; cancer; diabetes; autoimmune or inflammatory disorders; and disorders of coagulation) were used for comparison. TEG was performed alone and with the addition of 75 and 150 ng/mL tissue plasminogen activator (tPA) to quantify fibrinolysis resistance (tPA-challenged TEG).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.soard.2019.03.048>.

Results: The bariatric surgery cohort had a median age of 40.5 years, a median body mass index of 44.6 kg/m², and 90% female patients. Median body mass index reduced significantly 6 months post surgery but remained elevated compared with the HS group (31.4 versus 25.4 kg/m², $P < .0001$). At 6 months post surgery, subjects had longer reaction time (mean difference, 1.3; $P = .02$), lower maximum amplitude (-2.4 , $P = .01$), and increased fibrinolysis with low-dose (3.1, $P < .0001$) and high-dose tPA-challenged TEG (9, $P < .0001$). Compared with HS, the postsurgery TEG values were still more likely to be abnormal (all $P < .05$).

Conclusions: Patients with morbid obesity form stronger clots more rapidly and are more resistant to fibrinolysis than subjects without obesity. Bariatric surgery significantly improved the hypercoagulable

Keywords

Fibrinolysis; Thromboelastography; Venous thromboembolism; Thrombosis; Coagulopathy; Morbid obesity; Bariatric surgery

Morbid obesity (body mass index [BMI] ≥ 40 kg/m²) has increased 4-fold over the last 20 years in the United States, costing an estimated \$200 billion annually [1,2]. Obesity (BMI ≥ 30 kg/m²) is associated with an increased risk of venous thromboembolism (VTE), and this risk is further increased in patients with BMI ≥ 40 kg/m² undergoing bariatric surgery [2,3]. Proposed mechanisms include a chronic inflammatory state leading to hypercoagulability and fibrinolytic dysfunction [4,5]. Increased levels of coagulation factors, inflammatory proteins, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) in patients with morbid obesity have also been documented, and BMI reduction reduces the plasma concentrations of coagulation factors and PAI-1 toward normal ranges [4,6,7]. Although it is inferred that these markers correlate with clot formation and breakdown, few studies have measured whole blood clot formation characteristics in patients with morbid obesity, and no large studies have evaluated how these characteristics are affected by surgical weight loss [8-10]. The cell-based model of hemostasis provides a rationale for why whole blood assays are optimal for determining coagulation abnormalities [11]. Unlike conventional coagulation assays, whole blood viscoelastic assays can measure hypercoagulability and quantify resistance to fibrinolysis [11,12].

Specifically, viscoelastic assays, namely thromboelastography (TEG) and rotational thromboelastometry, provide functional measurements of each step of clot dynamics. These tools detect deflection of a pin within a cup containing whole blood during clot formation and degradation and translate the degree of deflection into a measurement of clot dynamics [13]. These measurements identify the presence of a hypocoagulable state with delayed clot formation, decreased clot strength, and enhanced clot degradation, such as that seen in severely injured trauma patients [14]. Similarly, these assays can also detect hypercoagulable states, with rapid clot formation and increased clot strength, such as the prothrombotic state seen with malignant neoplasms [15]. As a result, the identification of hypercoagulable states via TEG is now being used to direct VTE prophylaxis in a variety of diseases [16,17].

The aim of our study was to measure clotting kinetics using TEG in morbid obesity before and after bariatric surgery. Given the proinflammatory state and increases in coagulation

factors and antifibrinolytic proteins that occur with obesity, we hypothesize the following: (1) persons with morbid obesity exhibit a prothrombotic state with significant impairment of fibrinolysis, and (2) the obesity-related hypercoagulable state improves after bariatric surgery.

Methods

To test the hypotheses, we developed a 3-step experiment as follows:

Experiment 1

Hypothesis 1—Patients with morbid obesity undergoing bariatric surgery are more likely than individuals without obesity to have abnormalities of clot formation and fibrinolysis.

Setting and Subjects—This study was completed at a single bariatric center of excellence from May 2015 to November 2016 and is a retrospective comparison of prospectively obtained data. Patients with obesity were prospectively enrolled at the bariatric surgery preoperative visit and seen again by a research assistant at their 6-month clinic follow-up. This study was approved by the Colorado Multiple Institutional Review Board (COMIRB # 15-0040). For healthy controls, 75 healthy subjects (HS) were prospectively recruited from an outpatient clinic from May 2014 to November 2014 under a separate protocol approved by the COMIRB (#14-0366). These data were collected to identify the normal TEG ranges for healthy adults to provide a contextual comparison for other disease states. Exclusions included liver, cardiovascular, or kidney disease; cancer; diabetes; autoimmune or inflammatory disorders; disorders of coagulation; obesity (BMI ≥ 30); infection; recent surgery; injury; or transfusions.

Thromboelastography (TEG)—Venous blood was collected in citrated tubes, recalcified, and assayed at room temperature in 20–120 minutes as follows: (1) whole blood and (2) whole blood with the addition of 75 and 150 ng/mL of tissue plasminogen activator (tPA, lyophilized human tPA, Molecular Innovations, Novi, MI) for the tPA-challenge TEG, which reflects the relative sensitivity or resistance to tPA-mediated fibrinolysis [18]. TEG (TEG 5000 Thrombelastograph Hemostasis Analyzer, Haemonetics, Niles, IL) provides the following measurements: reaction time (R time [seconds]) representing time to clot formation and reflecting procoagulant and anticoagulant proteins concentrations; angle (degrees) representing clot formation speed and reflecting fibrin crosslinking; maximum amplitude (MA [mm]) representing maximum clot strength and reflecting concentration and function of platelets and fibrinogen; percent fibrinolysis at 30 minutes post-MA (LY30 [%]) reflecting clot dissolution; and the LY30 with the aforementioned tPA-challenged TEG.

Analysis—Univariate analysis for numeric variables used t tests or Wilcoxon tests as appropriate. Categorical variables were compared via χ^2 or Fisher exact tests as appropriate. All tests were 2-tailed, with significance at $P < .05$. Numerical variables were reported as median and interquartile or as mean with standard deviation.

Experiment 2

Hypothesis 2.1—Compared with prebariatric surgery, patients with morbid obesity experience a reduction in clot formation and fibrinolysis abnormalities 6 months post surgery.

Hypothesis 2.2—Compared with HS, postbariatric surgery reduces but does not normalize coagulation abnormalities.

Subjects—For hypothesis 2.1, we compared prebariatric and 6 months postbariatric surgery TEG data ($n = 36$). For hypothesis 2.2, we compared the postbariatric surgery measurements with the previously described HS group ($n = 75$).

Statistical Analysis—Univariate analysis was conducted using paired t tests for the hypothesis 2.1 and with t tests or Wilcoxon tests for hypothesis 2.2.

Experiment 3

As a hypothesis-generating pilot study, targeted proteomic analysis was completed on 15 preoperative patients and compared with 15 samples from a separate cohort of postoperative bariatric surgery patients. Mass spectrometry was used to analyze the chemical species in the plasma, specifically targeting 120 coagulation-related proteins. The specific methods are described in detail in Supplement.

Proteomics sample collection—Platelet-free plasma-citrated samples were prepared for proteomic analysis within 1 hour of collection by a 2-step centrifugation process in vacuum containers. Samples were spun at 5000 g at 4°C for 15 minutes to remove all cellular contaminants; the supernatant was decanted and respun at 12,500 g for 6 minutes to remove acellular debris. The supernatant plasma was immediately flash-frozen in liquid nitrogen and stored at −80°C.

Statistical analysis—Metaboanalyst was used to perform multivariate statistical analysis as described [19]. Data were log transformed and samples were normalized by sum. Univariate analysis was conducted using t tests or Wilcoxon tests for numeric variables depending on whether the variable was normally distributed or skewed.

Results

Experiment 1

Experiment 1: Subjects with morbid obesity are hypercoagulable with diminished fibrinolysis—Of 96 patients initially enrolled before bariatric surgery, 72 had preoperative TEG data (Fig. 1). Twenty-five patients (35%) underwent sleeve-gastrectomy. Compared with HS, the cohort undergoing bariatric surgery was older, more likely to be female, and had a higher BMI (Table 1). Also, bariatric surgery patients had more rapid clot formation (shorter R time, increased angle), stronger clots (increased MA), and diminished fibrinolysis (lower LY30 and tPA-challenge LY30 [Table 2]).

Experiment 2

Experiment 2.1: Weight loss results in improvement in hypercoagulable profile

—Overall, 36 patients had pre- and postbariatric surgery samples (Fig. 1). After bariatric surgery, the median BMI decreased to 31.4 kg/m² (range, 29.3–33.3 kg/m²) with a mean percent excess weight loss (%EWL) of 64.6% (55.4%–72.9%).

Compared with prebariatric values, TEG values 6 months after bariatric surgery trended toward a less hypercoagulable state with a longer R time, decreased MA, and decreased angle, although this did not reach statistical significance (Table 3). Although the 6-month follow-up LY30 did not differ from the preoperative value, the tPA-challenge LY30 showed a significant decrease. In addition, several differences were noted in clinical values after bariatric surgery (Table 3).

Experiment 2.2: Postbariatric patients remain hypercoagulable compared with healthy controls

—Despite significant weight loss (median %EWL=64.6%), postbariatric surgery TEG measurements remained hypercoagulable with diminished fibrinolysis compared with the HS group (Table 4).

Experiment 3: Proteomic analysis of coagulation-regulated proteins

Overall, 9 (8%) of 120 proteins were significantly different before and after bariatric surgery based on targeted proteomics. A principal component analysis found that overall, plasma proteomes were similar between the 2 groups (supplemental Fig. 1A); however, supervised clustering demonstrates two distinct proteomic signatures (supplemental Fig. 1B), as demonstrated by proteins listed in the Variable Importance in Projection (supplemental Fig. 1C). The generated heat map (supplemental Fig. 2) illustrates the 25 proteins with the greatest difference between the pre- and postbariatric surgery groups. Unsurprisingly, C-reactive protein, an inflammatory marker, was significantly lower in the postbariatric surgery group (22.1 versus 64.3, $P < .01$). Although the PAI-1 relative concentration was not significantly different between groups (4.14 versus 4.19, $P = .95$), vitronectin (314 versus 254, $P < .01$) and fibronectin (69.3 versus 53.7, $P < .01$) were significantly higher in the prebariatric surgery group compared with the postbariatric surgery group.

Discussion

Our study identified a hypercoagulable, hypofibrinolytic state before weight loss surgery in patients with morbid obesity. Postoperatively, these patients achieved a median %EWL comparable to a published series [20]. In addition, although they showed decreased clot formation and regained fibrinolytic activity, the patients continued to exhibit some fibrinolytic dysfunction compared with healthy volunteers. It should be noted, however, that patients undergoing bariatric surgery were significantly older than healthy subjects and more likely to be women, which could account for some of the differences in coagulation.

Studies suggest the mechanism for increased thrombotic risk in patients with morbid obesity includes a prothrombotic state combined with fibrinolytic dysfunction; although, they did not use viscoelastic assays [3,6,21]. There are few studies reporting the use of viscoelastic assays to evaluate obesity-related coagulation abnormalities, and although there is evidence

of a prothrombotic state, there are no abnormalities reported in fibrinolysis nor any evaluations of how coagulation is affected by bariatric surgery [8,22].

A decreased fibrinolytic response to the addition of tPA suggests an increase in one of the fibrinolytic pathway inhibitors and likely contributes to increased VTE risk. Impaired fibrinolysis has been identified as a major contributor to VTE risk in the patients with morbid obesity. PAI-1 is an inhibitor of fibrinolysis and binds to tPA, preventing tPA-mediated conversion of plasminogen to plasmin. PAI-1 is a serine protease inhibitor (serpin) that is expressed in the liver, endothelium, and adipose tissue, and PAI-1 levels are increased in patients with metabolic syndrome and obesity [23]. Furthermore, adipocyte PAI-1 expression is increased in patients with central obesity, and impaired fibrinolysis is linked to chronic inflammation and is at least in part due to tumor necrosis factor α increasing PAI-1 expression [24,25].

Although the targeted proteomic analysis did not identify a difference in PAI-1 levels between the pre- and postbariatric surgery groups, there was a significant reduction in vitronectin, a cofactor of PAI-1 that stabilizes the active form, increasing PAI-1 half-life [26,27]. Furthermore, vitronectin binds to antithrombin, competing with heparin and thus reducing the inactivation rate of thrombin and factor Xa [28].

In addition to a decrease in vitronectin, targeted proteomics also demonstrated a significant decrease in fibronectin, an important component of the fibrin clot, binding to fibrin both through covalent and noncovalent interactions [29]. This binding has been shown to increase the rate of fibrin clot formation and alter the density of fibers within the fibrin matrices. Fibronectin binding has also been shown to increase platelet binding in clots [30]. Thus, a decrease in fibronectin may explain the difference in angle and MA after bariatric surgery.

Morbid obesity is associated with chronic inflammation secondary to activated macrophages and inflammatory cytokines such as tumor necrosis factor α , interleukin 6, and interleukin 1 β released by adipocytes [21,31]. These cytokines maintain an inflammatory state in the liver and endothelium that promotes activation of prothrombotic pathways resulting in increased thrombin generation and platelet activation [32]. Plasma levels of other factors like fibrinogen, factor VIII, and von Willebrand Factor are also elevated [33]. Because fibrinogen function and platelet activation are thought to correlate with increases in angle and MA, respectively, these findings are in line with current literature [34].

Compared with healthy controls, the postoperative bariatric surgery group still showed some hypercoagulability. It is possible that the postbariatric surgery cohort may approach that of a control group without obesity as patients continue to lose weight and the inflammatory state continues to improve. Weight loss has been shown to nadir around 24 months after surgery, and the majority of the postoperative group has not yet reached this time point [35]. In addition, changes in other comorbidities such as diabetes or hypercholesterolemia may underlie these changes in coagulation rather than weight loss directly. Several other confounders may reflect the differences between the group undergoing bariatric surgery and the healthy control cohort. Specifically, the group undergoing bariatric surgery was older and

with a higher percentage of women, both of which are associated with a more hypercoagulable profile [36].

Conclusions

Morbid obesity is associated with the formation of stronger clots, formation at a faster rate, and diminished fibrinolysis. The fibrinolytic dysfunction in patients with morbid obesity appears to improve with weight loss and is associated with decreased vitronectin, which likely contributes to a reduction in PAI-1 activity. Clot formation and strength remained elevated at least 6 months after bariatric surgery compared with controls without obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. CONSORT diagram of patients lost to follow-up and with absent data. TEG = thromboelastography.

Table 1

Demographic data for the bariatric surgery group compared with the HS group

	Bariatric surgery group (n = 72)	HS control group (n = 75)	P value
Age, median (IQR), yr	40.5 (31–50)	30 (26–38)	<.0001
BMI, median (IQR), kg/m ²	44.6 (40.6–48.7)	25.4 (22.8–27.3)	<.0001
Female, No. (%)	65 (90)	41 (55)	.0004
Hypertension, No. (%)	31 (43)	0	<.0001
Type 2 diabetes, No. (%)	17 (24)	0	<.0001
Taking aspirin, No. (%)	5 (14)	0	.001
Non-ASA NSAIDs, No. (%)	24 (33)	0	<.0001
Statins, No. (%)	6 (17)	0	.0003
Non-ASA antiplatelet meds, No. (%)	0	0	-
Oral anticoagulants, No. (%)	0	0	-

HS = healthy subject; IQR = interquartile range; BMI = body mass index; ASA = aspirin; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 2

Comparison of coagulation profile of prebariatric surgery group and healthy control group

	Prebariatric surgery, median (IQR) (n = 72)	Healthy controls, median (IQR) (n = 75)	P value
R time (seconds)	11.2 (9.9–12.9)	14.3 (13.2–16.5)	<.0001
Angle (degrees)	53.4 (47.4–59.5)	42.4 (38.9–50.2)	<.0001
MA (mm)	67.5 (64.1–70.0)	55.5 (52.0–59.5)	<.0001
LY30(%)	0.6 (0.0–1.1)	1.2 (0.7–2.4)	<.0001
tPA-75 LY30 (%)	1.5 (0.8–2.8)	5.3 (3.1–7.2)	<.0001
tPA-150 LY30 (%)	5.8 (2.6–9.9)	38.4 (20.5–52.3)	<.0001

R time = reaction time; MA = maximal amplitude; LY30 = lysis 30 minutes after MA; tPA = tissue plasminogen activator; IQR = interquartile range.

Table 3

Thrombelastography profile before and 9 months after bariatric surgery

	N	Prebariatric surgery, median (IQR)	Postbariatric surgery, median (IQR)	Mean difference (SD)	P value
Thrombelastography					
R time (seconds)	36	11.3 (9.3–13.1)	12.4 (10.8–14.4)	1.3 (3.3)	.02
Angle (degrees)	36	54.0 (46.2–60.5)	49.2 (44.4–54.9)	–2.8 (8.8)	.07
MA (mm)	36	67.5 (62.9–70.4)	65.5 (60.0–68.5)	–2.4 (5.2)	.01
LY30 (%)	36	0.7 (0.03–1.2)	0.7 (0.1–1.5)	0.4 (0.9)	.33
tPA-75 LY30 (%)	36	1.4 (0.8–2.7)	4.5 (1.7–6.7)	1.2 (5.6)	<.0001
tPA-150 LY30 (%)	36	4.5 (2.6–9.1)	13.0 (5.9–21.3)	4.4 (13.8)	.0003
Clinical lab variables					
CRP (mg/dL)	31	8.8 (5.6–22.1)	3.3 (1.2–5.0)	–8.2 (7.8)	<.0001
Hemoglobin A1c (%)	30	5.8 (5.5–6.4)	5.5 (5.1–5.8)	0.65 (1.1)	.0015
Creatinine (mg/dL)	32	0.75 (0.68–0.87)	0.68 (0.62–0.82)	–0.5 (0.1)	.02

R time = reaction time; MA = maximal amplitude; LY30 = lysis 30 minutes after MA; tPA = tissue plasminogen activator; CRP = C reactive protein; IQR = interquartile range; A1c = glycated hemoglobin.

Table 4

Coagulation profile of the postoperative and HS control group

	Postoperative median (IQR) (n = 36)	HS group median (IQR) (n = 75)	P value
R time (seconds)	12.4 (10.8–14.4)	14.3 (13.2–16.5)	<.0001
Angle (degrees)	49.2 (44.4–54.9)	42.4 (38.9–50.2)	<.0001
MA (mm)	65.5 (60–68.5)	55.5 (52.0–59.5)	<.0001
LY30 (%)	0.7 (0.1–1.5)	1.2 (0.7–2.4)	.0013
tPA-75 LY30 (%)	4.5 (1.7–6.7)	5.3 (3.1–7.2)	.29
tPA-150 LY30 (%)	13.0 (5.9–21.3)	38.4 (20.5–52.3)	<.0001

R time = reaction time; MA = maximal amplitude; LY30 = lysis 30 minutes after MA; tPA = tissue plasminogen activator; IQR = interquartile range.