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Reductions in plasmin inhibitor and fibrinogen predict the improved fibrin clot lysis six months after obesity surgery

Running title: Predictors of changes in fibrin clot lysis

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Keywords

Bariatric surgery, fibrinolysis, glucose, hemostasis, lipids, obesity

What is already known about this subject?

- Many metabolic and prothrombotic variables are reduced after obesity surgery
- *In vitro* fibrin clot lysis is increased after obesity surgery
- The increase in fibrin clot lysis after obesity surgery is only partly determined by a decrease in fibrinogen, and other determinants need to be identified

What this study adds

- Levels of factor XIII and the fibrinolytic enzymes thrombin activatable fibrinolysis inhibitor, plasminogen, and plasmin inhibitor are reduced after obesity surgery
- The increase in fibrin clot lysis after obesity surgery is predicted by reductions in plasmin inhibitor and fibrinogen, and these are predicted by reductions in glucose, cholesterol, and interleukin 6
- Targeting plasmin inhibitor and fibrinogen, by reducing metabolic variables such as glucose, cholesterol, and interleukin 6, has a profibrinolytic effect in obesity

Abstract

Background: Prothrombotic and metabolic variables are decreased after obesity surgery, and fibrin clot lysis is increased. It is unknown how fibrinolytic variables are affected, and whether fibrinolytic and metabolic changes predict the enhanced clot lysis.

Objective: To determine fibrinolytic biomarkers before and 6 months after Roux-en-Y gastric bypass (RYGB) and to identify predictors of the RYGB-induced increase in clot lysis.

Methods: Women (n=42) and men (n=18) with obesity underwent RYGB, and factor XIII (FXIII), thrombin activatable fibrinolysis inhibitor (TAFI), plasminogen, and plasmin inhibitor (PI) were measured before and 6 months after surgery. Regression analyses identified determinants of the RYGB-induced increase in clot lysis among changes in fibrinogen and in fibrinolytic and metabolic variables.

Results: After RYGB, FXIII, TAFI, plasminogen, and PI were reduced ($p<0.0005$). Reductions in PI ($\beta=-0.59$) and fibrinogen ($\beta=-0.35$), together with age ($\beta=-0.22$) and male sex ($\beta=0.22$), predicted the enhanced clot lysis with the model explaining 56% ($p<0.0005$). Predictors of the reduction in PI were reductions in cholesterol ($\beta=0.37$) and glucose ($\beta=0.29$), together with male sex ($\beta=-0.28$), whereas reductions in fibrinogen were predicted by lowering of interleukin-6 ($\beta=0.32$).

Conclusion: Fibrinolytic variables were reduced 6 months after RYGB. Targeting PI and fibrinogen, by reducing metabolic variables such as glucose, cholesterol, and interleukin 6, has a profibrinolytic effect in obesity.

Abbreviations

IL-6	Interleukin 6
TNF-α	Tumor necrosis factor alpha
TF	Tissue factor
PAI-1	Plasminogen activator inhibitor type 1
CVD	Cardiovascular disease
RYGB	Roux-en-Y gastric bypass
t-PA	Tissue plasminogen activator
FXIII	Factor XIII
TAFI	Thrombin activatable fibrinolysis inhibitor
PI	Plasmin inhibitor
BMI	Body mass index
LDL	Low density lipoprotein
HbA1c	Hemoglobin A1c

Introduction

The prevalence of obesity continues to increase worldwide (1), and in 2015 a total of 100 million children and 600 million adults suffered from obesity (2). Obesity is characterized by an excessive amount of adipose tissue, an endocrine organ that secretes a high number of proinflammatory cytokines, e.g. interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) (3-6). These cytokines contribute to tip the hemostatic balance towards a prothrombotic state (7-11) by stimulating the endothelial synthesis of tissue factor (TF) and plasminogen activator inhibitor type 1 (PAI-1) and the hepatic production of coagulation factors, such as fibrinogen, factor VII, and factor FVIII (8, 10). As a consequence, obesity is accompanied by increased levels of several prothrombotic biomarkers (12), and the consequence is an increased risk of cardiovascular disease (CVD) (13, 14).

The obesity-associated increased CVD risk can be reduced by obesity surgery (15, 16). We and others have demonstrated that prothrombotic variables, such as TF, fibrinogen, measures of thrombin generation, and PAI-1, are reduced after obesity surgery (12). Also, we have recently observed that 6 months after Roux-en-Y gastric bypass (RYGB), *in vitro* fibrin clot lysis is markedly increased, measures of fibrin clot structure, e.g. fiber mass-length ratio and fiber diameter, are reduced, and fiber density is increased (17). *In vitro* fibrin clot characteristics reflect the lysability and structure of a fibrin clot formed in a plasma system with and without the addition of tissue plasminogen activator (t-PA) (18). Several studies have consistently documented that low *in vitro* fibrin clot lysability is associated with a high CVD risk (19, 20).

Various genetic and environmental conditions affect *in vitro* fibrin clot properties, e.g. genetic polymorphisms, diabetes, medication, smoking, and oral contraceptives partly due to an

effect on the plasma fibrinogen concentration, which is an important precursor and determinant of *in vitro* fibrin clot formation (19, 21-23). The changes in fibrin clot properties observed after RYGB are, however, not only caused by a reduction in the concentration of fibrinogen (17), and more studies are needed to identify determinants of the surgery-induced changes.

Besides changes in fibrinogen, the most obvious predictors of changes in *in vitro* fibrin clot lysis are changes in factor XIII (FXIII), which cross-links and stabilizes the fibrin fibers within the fibrin clot, and the fibrinolytic enzymes thrombin activatable fibrinolysis inhibitor (TAFI), plasminogen, plasmin inhibitor (PI), and PAI-1. Among these variables only fibrinogen and PAI-1 have been studied after obesity surgery (17). Further, triglycerides, cholesterols, glucose, IL-6, and other metabolic variables are significantly reduced after obesity surgery (24, 25), and it is unknown whether metabolic improvements are associated with changes in the fibrinolytic variables. Our aim was therefore to measure FXIII, TAFI, plasminogen, and PI before and 6 months after RYGB and to identify predictors of the RYGB-induced changes in fibrin clot lysis and structure among changes in fibrinolytic variables. Further, we identified predictors of the fibrinolytic changes among alterations in metabolic variables.

Materials and Methods

The present sub-study is part of a larger study investigating the effects of supervised physical training following RYGB on weight loss (24), muscle strength and aerobic capacity (26), physical activity and quality of life (27), and markers of CVD (17, 25). Results reported in this paper are based on secondary outcome variables and only include samples before and 6 months after

bariatric surgery, i.e. relatively early after bariatric surgery. All subjects gave oral and written informed consent, and the study was conducted according to the Helsinki Declaration, approved by the local Ethics Committee (Project-ID: S-20120112), and registered at http:/www.clinicalTrials.gov (NCT01690728).

Participants and study design

The study design has been described in detail elsewhere (24). In the present study, we included 42 women and 18 men, mean age 42.3 years, who were eligible for RYGB according to the national and international guidelines, as well as Danish criteria regulating free access to bariatric surgery (body mass index (BMI) > 35 kg/m^2 with obesity related disease or BMI > 50 kg/m^2 with obesity related social or physical complications). Major co-morbidities were hypertension (n=27), type 2 diabetes (n=18), and dyslipidemia (n=12), and accordingly major medications were antihypertensives (n=27), antidiabetics (n=18), and lipid lowering drugs (n=11). Nineteen patients did not receive any medication (17). Only non-smoking patients were included. The patients underwent RYGB at the University Hospital of Southern Denmark, and blood samples were obtained before and 6 months after RYGB. We excluded patients who received anticoagulant medication or hormone replacement therapy/oral contraceptives.

Laparoscopic RYGB surgery was performed by one of three surgeons at the Department of Surgery, University Hospital of Southern Denmark, with a 20-30 ml gastric pouch, a 60 cm bilio-pancreatic limb and a Roux limb of 150 cm (24).

The subjects' characteristics before and 6 months after obesity surgery are presented in Table 1. Also, previously published results relevant for the present sub-study are included in Table 1 and show that measures of body weight, blood lipids, glucose (24), inflammation (25), and hemostasis, including fibrinogen, fibrin clot lysis and structure (17), decrease significantly after surgery.

Blood sampling

Venous blood samples were collected between 7.45 and 8.30 in the morning after at least 10 hours of fasting and 15 minutes of rest in a supine position. For the present study, all samples were collected in trisodium citrate tubes (0.109 M Na_3Citrate, BD Ref: 363048). Immediately after sampling, platelet poor plasma was prepared by centrifugation for 20 minutes at 2000 x g (20°C). Plasma was rapidly frozen and stored at -80°C until analyzed.

Plasma analyses

Samples were thawed in a water bath at 37°C and analyzed in one series for each individual. The functional activity of FXIII was determined with the Berichrome Factor XIII kit (Siemens Healthcare Diagnostics). Concentrations of TAFI were determined with the VisuLize TAFI antigen kit (Affinity Biologicals, Ontario, Canada). The activities of plasminogen and PI were determined using chromogenic assays with the HemosIL Plasminogen and the HemosIL Plasmin Inhibitor kit, respectively, using the ACL TOP 350 analyzer (Instrumentation Laboratories, Milan, Italy). Analytical methods used for previously reported variables (Table 1) are described elsewhere (17, 24, 25).

Statistics

Sample size was determined for the primary effect variable body weight, as previously presented (24). Effects of RYGB were analyzed using a paired t-test due to normally distributed variables. The results are presented as mean and 95% confidence interval.

We used univariate regression analyses to determined associations between surgery-induced changes in fibrinolytic variables and changes in measures of fibrin clot lysis and structure, and this was followed by multivariate linear regression analyses with changes in fibrinolytic measures as independent variables and changes in fibrin clot lysis or structure as dependent variables. Next, univariate regression analyses were performed between changes in metabolic variables and changes in the significant fibrinolytic determinants from the first multivariate analyses. This was followed by multivariate regression analyses with changes in metabolic measures as independent variables and changes in the fibrinolytic determinants as dependent variables. For all multivariate regression analyses, only variables with $p<0.05$ in the univariate regression analyses were included. All analyses were adjusted for age, sex (female=0, male=1), and medication (use/no use). Among highly correlated variables in the univariate analyses (total cholesterol/low density lipoprotein (LDL)-cholesterol and glucose/hemoglobin 1Ac (HbA1c)), only the variable most highly associated with the dependent variable was included in the multivariate analyses. Standard (enter) and stepwise (backward, variables with $p>0.01$ were stepwise excluded from the model) multivariate analyses were performed. The models gave similar results, and only results from standard multivariate regressions are presented.

A p-value of less than 0.05 was considered significant. The SPSS program (version 24; IBM SPSS Inc., Chicago, IL, USA) was used for all the statistical analyses.

Results

Six months after RYGB we observed highly significant reductions in FXIII, TAFI, plasminogen, and PI (Table 2). These results were confirmed in the subgroup of 19 patients who were not receiving any medication (not shown). Table 3 presents the results of the univariate regression analyses between changes in fibrinolytic variables and changes in measures of fibrin clot lysis showing that reductions in FXIII, plasminogen, PI, and fibrinogen significantly correlated with the increase in lysis, and the best predictor was PI (R^2=0.35, p<0.0005). The corresponding multivariate regression analysis with these variables as independent variables and changes in fibrin clot lysis as dependent variable showed that significant predictors of increased clot lysis were reductions in PI (β=-0.59, p<0.0005) and fibrinogen (β=-0.35, p=0.001). Also, age (β=-0.22, p=0.036) and male sex (β=0.22, p=0.034) were independently related to the increase in lysis. The multivariate model explained 56% (R^2=0.56, p<0.0005) of the increase in clot lysis after obesity surgery.

Table 4 presents univariate associations between changes in metabolic variables and changes in PI and fibrinogen, respectively. Reductions in PI were significantly associated with decreased lipids and measures of glucose with the best predictor being total cholesterol (R^2=0.24, p<0.0005), whereas reductions in fibrinogen were significantly associated with the decrease in IL-6 (best predictor, R^2=0.13, p=0.005), triglycerides, HbA1c, and glucose. The corresponding

multivariate regression analyses showed that significant predictors of reductions in PI were reductions in total cholesterol (β=0.37, p=0.010) and glucose (β=0.29, p=0.024), together with male sex (β=-0.28, p=0.020), with the model explaining 44% (p<0.0005) of the reduction in PI after surgery. The only significant predictor of the reduced fibrinogen was the decrease in IL-6 (β=0.32, p=0.015), and the model explained 25% (p=0.016) of the reduction in fibrinogen after surgery.

In the multivariate analyses, changes in fibrinogen predicted changes in measures of fibrin clot structure (fiber density, β=-0.47, p<0.0005; fiber diameter, β=0.40, p=0.004).

Discussion

In the present study, we demonstrated that FXIII, TAFI, plasminogen, and PI were lowered 6 months after RYGB, and that the enhanced *in vitro* clot lysis (17) was predicted by the decrease in PI and fibrinogen. The effect on lysis was sex-specific with a more pronounced increase in lysis in men. Further, the reduction in PI was determined by reductions in cholesterol and glucose and by male sex, while the reduction in fibrinogen was determined by the decrease in IL-6. Changes in measures of fibrin clot structure were only predicted by changes in fibrinogen.

This is the first study measuring FXIII, TAFI, plasminogen, and PI after obesity surgery and addressing determinants of the improved *in vitro* clot lysis after RYGB (17). Thus, RYGB is accompanied by reductions in fibrinogen concentration and FXIII activity, and the fibrinolytic potential is increased due to a pronounced decrease in PAI-1 (17), TAFI, and PI. This may lead to a diminished FXIII-mediated cross-linking of PI (28) and TAFI (29) to the fibrin clot. In contrast, due to the reduction in plasminogen, less plasmin will be available at the surface of the fibrin clot.

However, the net result is an improved clot lysis, and the multivariate model suggests that reductions in PI and fibrinogen are the most important determinants. This is supported by recent results in type 2 diabetes patients showing that independent predictors of clot lysis are the extent of PI incorporation in the fibrin clot, the plasma concentration of fibrinogen, and sex (30).

In people with obesity, the levels of glucose and cholesterol in blood are increased (24), but it is unknown whether this increases the inhibitory capacity of PI. Plasmin inhibitor contains four glycosylation sites (31, 32), and protein glycation might diminish fibrinolysis. Thus, glycation of fibrinogen reduces the susceptibility of fibrin to plasmin degradation (33), and glycation of plasminogen leads to reduced plasmin generation (34). Also, increased concentrations of HbA1c are associated with prothrombotic fibrin clots (35, 36) and with increased cross-linking of PI to fibrin (30, 36). To our knowledge, no data exists on PI glycation, but our results tentatively suggest that the reduction in glucose (and HbA1) after RYGB might decrease the inhibitory capacity of PI, perhaps due to diminished protein glycation. Our results also demonstrate that lowering of cholesterol after RYGB independently predicts the reduction in PI. No other study has looked at the association between cholesterol and the inhibitory capacity of PI, but a prolonged clot lysis time was previously associated with low HDL-cholesterol (37) and high LDL-cholesterol (38), and Pieters et al suggested that LDL-cholesterol can bind to fibrin clots thereby hindering the action of lytic enzymes, a new role that deserves further investigation (38).

In the multivariate analysis, only the decrease in IL-6 was associated with the decrease in fibrinogen. This is most likely a consequence of the reduced fat mass after RYGB (24). Adipocytes synthesize pro-inflammatory cytokines such as IL-6, stimulating the hepatic synthesis of e.g. C-

reactive protein and fibrinogen (8, 10). It might be speculated whether the hepatic effect of IL-6 also includes liver-derived proteins such as FXIII, TAFI, plasminogen, and PI, but we observed no associations between changes in IL-6 and changes in these variables (results not shown).

We observed independent sex-specific effects on changes in clot lysis after RYGB. A sex-specific effect on absolute values of clot lysis was previously observed. Thus, a prolonged lysis time was seen in women compared to men with type 2 diabetes (37), coronary artery disease (39), atrial fibrillation (40), and asymptomatic coronary artery calcification (41), and this might be mediated by increased incorporation of PI into the fibrin clot in women compared with men (30). In our study, sex was also an independent predictor of changes in PI, cautiously suggesting a more antithrombotic effect of obesity surgery in men than in women. More men than women had type 2 diabetes, but adjusting for diabetes did not remove the sex-specific effects (not shown).

Our findings on increased fibrinolysis after RYGB indicate a reduced thrombotic potential with a decreased CVD risk. Whether it also increases the risk of clinically relevant bleeding is unknown. The clinical relevance of our findings is difficult to predict from significant changes in fibrinolytic biomarkers, although biomarkers are valuable tools in understanding the mechanisms linking obesity surgery to fibrinolysis. Our findings from the regression analyses suggest that other factors than body weight reduction are determinants of fibrinolytic changes after obesity surgery. This is supported by the lack of significant associations between reduction in body weight and reduction in coagulation biomarkers after bariatric surgery (12). We focus on RYGB-induced changes in metabolic variables as possible predictors of changes in fibrinolysis, but the cause of these changes can be numerous and include the inevitably accompanying weight loss, changes in

medication, vitamin uptake or intake and in particular vitamin K, comorbidity, diet, and exercise, the negative energy balance during weight loss, and surgical complications.

A major strength of our study is the large increase in clot lysis after a surgical intervention providing the possibility of addressing predictors of intra-individual changes after weight loss and not only absolute values in a cross-sectional design. Study limitations are the high number of drugs given to the patients, although medicine/no medicine was not a significant predictor in the multivariate analyses. Although prolonged *in vitro* fibrin clot lysis is associated with CVD risk in several studies, fibrin formation and lysis are measured in the presence of high concentrations of thrombin and t-PA and in the absence of blood cells, thus deviating from *in vivo* fibrin formation. In support of our results, fibrinolysis was also increased 6 months after bariatric surgery when measured in whole blood by thromboelastography (42).

In conclusion, levels of FXIII, TAFI, plasminogen, and PI were reduced 6 months after RYGB, and reductions in PI and fibrinogen, together with age and sex, predicted the enhanced clot lysis. Among the metabolic variables, reductions in glucose and cholesterol predicted the decrease in PI, whereas the reduction in IL-6 predicted the decrease in fibrinogen (Figure 1). This indicates that targeting PI and fibrinogen by improving the metabolic state after RYGB, for example by reducing concentrations of glucose, cholesterol, and IL-6, is the most effective profibrinolytic strategy in obesity. Our study was a hypothesis-generating study, and possible mechanisms explaining the observed associations should be investigated in future studies.

Conflicts of interest

The authors have no conflicts of interest.

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Legends for tables and figure

Table 1: Mean values (95% confidence intervals) before surgery and 6 months after surgery were compared with a paired t-test (* p<0.05, ** p<0.01, *** p<0.001, **** p<0.0005). #Fibrin clot lysis and measures of fibrin structure were determined using turbidity measurements with and without addition of rt-PA according to the method described by Sjøland et al. (17, 18). BMI, body mass index; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; IL-6, interleukin 6; t-PA:Ag, tissue plasminogen activator antigen; PAI-1:Ag, plasminogen activator inhibitor type 1 antigen; M/L ratio, mass-length ratio. Subjects' characteristics were previously reported in Mundbjerg et al (24) and Stolberg et al (17, 25).

Table 2: Mean values and 95% confidence intervals before surgery and 6 months after surgery were compared with a paired t-test (**** p<0.0005). FXIII, factor XIII; TAFI, thrombin activatable fibrinolysis inhibitor.

Table 3: FXIII, factor XIII; TAFI, thrombin activatable fibrinolysis inhibitor; PAI-1:Ag, plasminogen activator inhibitor type 1 antigen; t-PA:Ag, tissue plasminogen activator antigen

Table 4: BMI, body mass index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; IL-6, interleukin 6.

Figure 1: Effects of obesity surgery on *in vitro* fibrin clot lysis

In the assay, thrombin is added in excess thereby quickly converting plasma fibrinogen into cross-linked fibrin in the presence of FXIIIa. Also, t-PA is added in excess and quickly activates plasminogen into plasmin. This takes place at the surface of the fibrin clot where plasminogen and t-PA bind to lysine residues on cross-linked fibrin. Inhibition of fibrinolysis is accomplished through plasma concentrations of PAI-1 (although here of minor importance due to the high concentration of t-PA) and by PI and TAFI, both being cross-linked to the fibrin clot by FXIIIa.

Variables identified as independent predictors in the multivariate analyses are shown in italics.

⟶ Activation; ⊸ inhibition; ↓ reduced after obesity surgery; ↑increased after obesity surgery. FXIII, factor XIII; TAFI, thrombin activatable fibrinolysis inhibitor; PI, plasmin inhibitor; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor type 1; IL-6, interleukin

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Table 1. Subjects' characteristics before and 6 months after obesity surgery

Variable	Pre-surgery (n=60)	Post-surgery (n=60)
Body weight (kg)	126.6 (121.2-132.0)	99.2 (94.4-103.9)****
BMI (kg/m^2)	43.0 (41.4-44.5)	33.7 (32.2-35.2)****
Abdominal fat volume (ml)	920 (839-1002)	508 (456-560)****
Total cholesterol (mmol/l)	4.48 (4.21-4.75)	3.94 (3.74-4.14)****
LDL cholesterol (mmol/l)	2.88 (2.65-3.11)	2.32 (2.15-2.49)****
HDL cholesterol (mmol/l)	1.03 (0.97-1.09)	1.14 (1.08-1.19)****
Triglycerides (mmol/l)	1.38 (1.22-1.53)	0.99 (0.90-1.08)****
Glucose (mmol/l)	6.22 (5.84-6.60)	5.52 (5.26-5.78)****
Insulin (mmol/l)	159.4 (131.6-187.4)	66.9 (55.2-78.6)****
HbA1c (mmol/l)	38.3 (35.9-40.8)	34.5 (33.1-35.8)****
HOMA-IR	6.18 (5.02-7.34)	2.31 (1.85-2.77)****
IL-6 (pg/ml)	4.10 (3.61-4.58)	2.71 (2.39-3.04)****
t-PA:Ag (ng/ml)	11.0 (9.7-12.3)	9.0 (7.6-10.4)****
PAI-1:Ag (ng/ml)	42.9 (37.0-48.8)	24.5 (21.7-27.3)****
Fibrinogen (µmol/l)	12.9 (12.3-13.6)	11.6 (11.0-12.2)****
Fibrin clot lysis (%)$^{\#}$	27.2 (23.6-30.8)	43.1 (38.4-47.8)****
Fiber M/L ratio (x10^{12} Da/cm)$^{\#}$	6.24 (6.00-6.48)	5.95 (5.75-6.16)***
Fiber diameter (µm)$^{\#}$	0.153 (0.148-0.157)	0.146 (0.142-0.149)****

Fiber mass density (x10^{22} Da/cm^3)#	3.47 (3.35-3.59)	3.54 (3.45-3.64)*

Table 2. Fibrinolytic variables before and 6 months after obesity surgery

Variable	Pre-surgery (n=60)	Post-surgery (n=60)
FXIII (%)	119 (113-126)	104 (99-110)****
TAFI (μg/ml)	11.9 (11.3-12.5)	11.2 (10.7-11.8)****
Plasminogen (%)	97 (93-101)	89 (86-93)****
Plasmin inhibitor (%)	97 (95-99)	91 (88-93)****

Table 3. Univariate regression analyses of *changes* in clot lysis (dependent variable) in relation to *changes* in fibrinolytic variables

Independent variables	R^2 (%)	Standardized β	p-value
FXIII (%)	0.11	-0.336	**0.009**
TAFI (µg/ml)	0.21	0.145	0.270
Plasminogen (%)	0.12	-0.346	**0.007**
Plasmin inhibitor (%)	0.35	-0.594	**<0.0005**
PAI:Ag (ng/ml)	0.09	-0.097	0.463
t-PA:Ag (ng/ml)	0.19	-0.136	0.298
Fibrinogen (µmol/l)	0.11	-0.336	**0.009**

Table 4. Univariate regression analyses of *changes* in plasmin inhibitor and fibrinogen (dependent variables) in relation to *changes* in metabolic variables

Independent variables	Plasmin inhibitor			Fibrinogen		
	R^2 (%)	β	p-value	R^2	β	p-value
Body weight (kg)	0.03	0.055	0.675	0.38	0.194	0.138
BMI (kg/m^2)	0.00	0.010	0.939	0.22	0.149	0.257
Abdominal fat (ml)	0.06	0.076	0.568	0.06	0.076	0.568
Waist/hip ratio	0.31	0.177	0.180	0.08	-0.088	0.506
HDL-cholesterol (mmol/l)	0.95	0.308	**0.017**	0.34	-0.185	0.158
LDL-cholesterol (mmol/l)	0.16	0.399	**0.002**	0.25	0.159	0.224
Total cholesterol (mmol/l)	0.24	0.487	**<0.0005**	0.09	0.092	0.483
Triglycerides (mmol/l)	0.15	0.391	**0.002**	0.69	-0.263	**0.042**
HbA1c (mmol/l)	0.11	0.326	**0.011**	0.82	-0.287	**0.026**
Glucose (mmol/l)	0.14	0.368	**0.004**	0.10	-0.317	**0.014**

Insulin (pmol/l)	0.06	-0.077	0.564	0.34	-0.183	0.164
HOMA-IR	0.00	-0.013	0.925	0.55	-0.235	0.073
IL-6 (pg/ml)	0.10	-0.102	0.437	0.13	0.355	**0.005**

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Section 1. Identifying Information

1. Given Name (First Name): Bibi Valgerdur
2. Surname (Last Name): Gram
3. Date: 30-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
   Corresponding Author's Name: Nadja Christensen

5. Manuscript Title
   Reductions in plasmin inhibitor and fibrinogen predict the improved fibrin clot lysis after obesity surgery

6. Manuscript Identifying Number (if you know it)

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Dr. Gram has nothing to disclose.

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Section 1. Identifying Information

1. Given Name (First Name): Peter
2. Surname (Last Name): Funch-Jensen
3. Date: 30-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
Corresponding Author's Name: Nadja Christensen

5. Manuscript Title
Reductions in plasmin inhibitor and fibrinogen predict the improved fibrin clot lysis after obesity surgery

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Section 1. Identifying Information

1. Given Name (First Name): Moniek P. M.
2. Surname (Last Name): de Maat
3. Date: 30-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
   Corresponding Author's Name: Nadja Christensen

5. Manuscript Title: Reductions in plasmin inhibitor and fibrinogen predict the improved fibrin clot lysis after obesity surgery

6. Manuscript Identifying Number (if you know it)

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

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Are there any relevant conflicts of interest? ☐ Yes ☑ No

Section 4. Intellectual Property -- Patents & Copyrights

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Section 1. Identifying Information

1. Given Name (First Name): Anna-Marie Bloch
2. Surname (Last Name): Münster
3. Date: 30-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
   Corresponding Author's Name: Nadja Christensen

5. Manuscript Title
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6. Manuscript Identifying Number (if you know it)

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Else Marie
2. Surname (Last Name): Bladbjerg
3. Date: 27-April-2020

4. Are you the corresponding author? ☐ Yes ☑ No
   Corresponding Author's Name: Nadja Christensen

5. Manuscript Title
   Reductions in plasmin inhibitor and fibrinogen predict the improved fibrin clot lysis after obesity surgery

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Dr. Bladbjerg has nothing to disclose.

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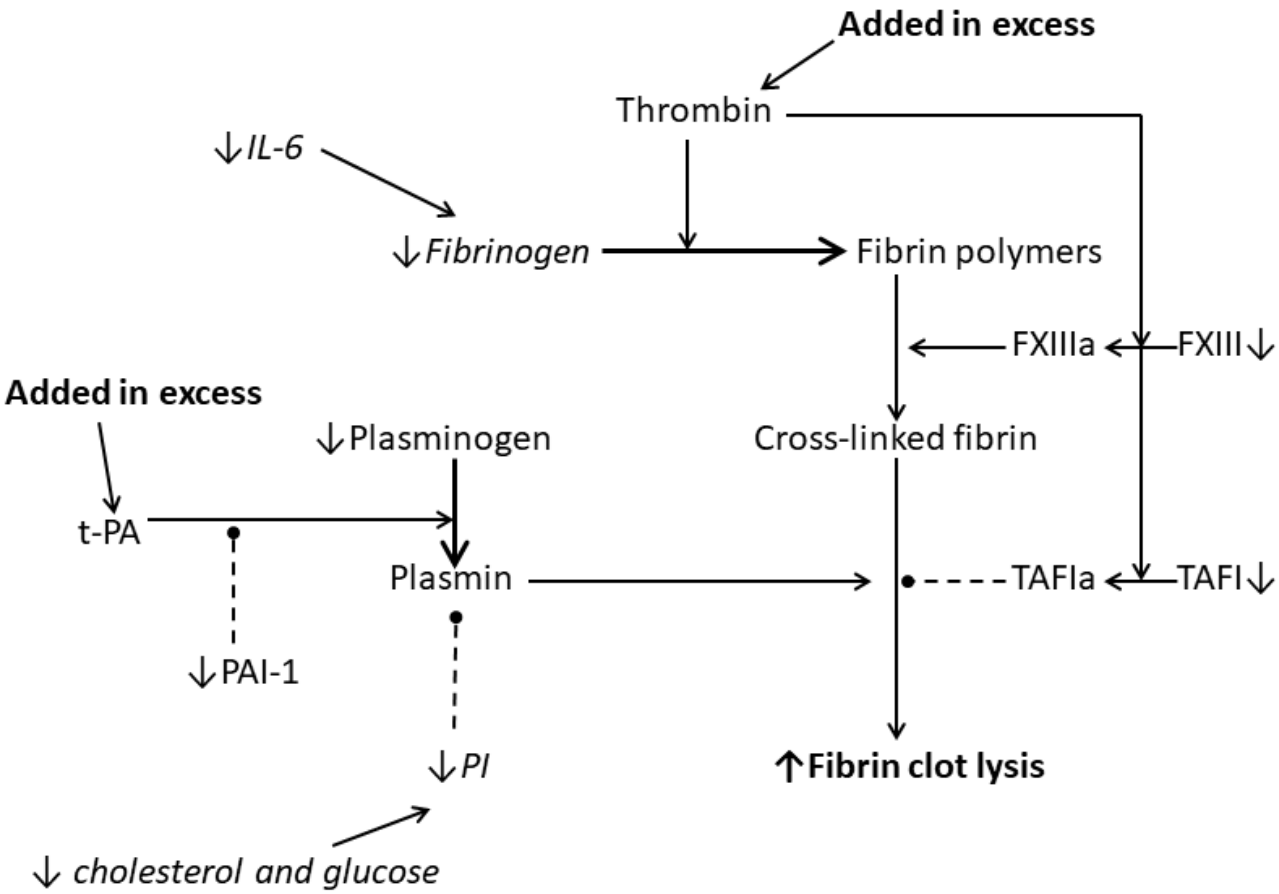
Figure 1



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