Thromboelastography values remain hypercoagulative 6 months after obesity surgery. A pilot study.

Running title: Hypercoagulation and obesity

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Abstract

Purpose: Obesity causes a prothrombotic state and is known as a predisposing factor for thromboembolic events. In this pilot study, we assessed the impact of surgery for obesity and the subsequent weight loss on blood coagulation using traditional coagulation tests and thromboelastography (TEG).

Material and Methods: We studied blood samples from 18 patients receiving bariatric surgery. Besides traditional blood coagulation tests and high-sensitivity C-reactive protein (hsCRP) as a marker of inflammation, the TEG parameters reaction time (R), kinetics time (K), angle (α), maximum amplitude (MA), clot strength (G), and lysis percent at 60 min (LY60) were determined preoperatively and on the first postoperative day and six months after surgery.

Results: Altogether, 54 samples were analyzed. The median MA (71.3 mm), G (12403.3 d/sc) and hsCRP (3.5 mg/l) were elevated preoperatively. The median hsCRP further increased on the first day postoperatively, but declined to the normal range six months after surgery, while MA and G remained elevated. In traditional coagulation tests, there was an increase in median fibrinogen and D-dimer postoperatively. D-dimer normalized (0.4 mg/l) during the study period, while the fibrinogen level (4.1 g/l) remained above the upper limit of normal.

Conclusions: Measured by TEG, patients receiving bariatric surgery have hemostatic abnormalities indicating hypercoagulation at the 6-month follow-up visit, suggesting an elevated risk for thromboembolic events for at least six months after surgery.

Keywords: TEG, Obesity, Morbid/surgery, Venous Thromboembolism/blood

Introduction

Obesity is a known predisposing factor for thromboembolic events [1-4]. In obese individuals, there is an up to five fold increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) with increasing body mass index (BMI) [1]. There are many explanations for this elevated risk such as inactivity, altered venous hemodynamics, and chronically elevated intra-abdominal pressure as well as endothelial dysfunction and hypercoagulability related to excess adipose tissue [5,6]. Hormones and cytokines produced by adipocytes induce a procoagulant and proinflammatory state, both of which may also play a role in thromboembolic events [2,7-9]. Furthermore, obesity is associated with lower limb venous diseases, which further predispose patients to DVT [5]. Obese patients may also have other etiologies for impaired venous return from the lower limbs such as chronically raised intra-abdominal pressure, inactivity, and immobility related to osteoarthritis [6].

Thromboelastography (TEG) provides information about the entire clotting system by measuring the viscoelastic properties of whole blood during the coagulation process. It has been used to diagnose coagulation disorders and to guide blood transfusions during major surgery, trauma, and postpartum hemorrhage [10-13]. However, it is also capable of detecting hypercoagulative states [14-16]. In patients undergoing bariatric surgery, TEG has been shown to be hypercoagulative at the time of the operation [4,17].

In this observational pilot study we assessed the impact of surgery for obesity on blood coagulation using traditional laboratory testing and TEG. According to our hypothesis, surgery for obesity and the subsequent weight loss will alter obesity-related hypercoagulation towards normal blood coagulation.

Materials and Methods

After approval by the Ethical Committee of the Northern Osthrobotnia Hospital District (reference number 100/2015), we recruited 18 patients aged 18-65 years with American Society of Anesthesiology (ASA) I-III, who underwent surgery for obesity in Oulu University Hospital between 2015 and 2016. Written informed consent was obtained from all participants. Patients who had a recent thromboembolic event (DVT or PE) or who were taking aspirin, warfarin, or any antiplatelet drug were excluded. Obesity was classified according to body mass index as obesity (BMI ≥30 kg/m^2), severe obesity (BMI 35-39.9 kg/m^2), morbid obesity (BMI 40-49.9 kg/m^2), and super obesity (BMI ≥50 kg/m^2). There were two (11%) patients with obesity, five (28%) patients with severe obesity, nine (50%) with morbid obesity, and two (11%) with super obesity . Patients received a fixed dose of enoxaparine 40 mg once daily as a thrombosis prophylaxis, beginning after the operation and continuing 10 days postoperatively except for in one patient who was given an elevated dose of 60 mg because the risk of DVT was estimated to be high.

Patients characteristics

Patient characteristics like age, gender, height, weight, ASA risk classification, comorbidities, type of surgery, duration of surgery, and the use of low molecular-weight heparin were recorded. BMI was calculated according to the formula BMI = weight (kg) ÷ (height [m])^2 before and six months after the operation. DVT or PE diagnosed during the study period was recorded, but not screened systematically.

Blood sampling

Blood samples were taken at three time points; the morning before entering the operation room (T1), on the first postoperative day (T2), and six months after the operation (T3). The traditional laboratory tests analyzed were hemoglobin, platelet count, thromboplastin time, International Normalized Ratio, fibrinogen, and D-dimer. In addition, we determined high sensitivity C reactive protein (hsCRP), which reflects inflammation [7-9]. From TEG parameters, we analyzed R (reaction time) and K (kinetics time), which reflect the initiation of coagulation; α (angle), MA (maximum amplitude), and G (clot strength), which reflect the clot formation; and Ly60, which reflects fibrinolysis at 60 min [18]. All blood samples were taken from an antebrachial vein using a normal venipuncture technique.

TEG analyses

TEG samples were collected into vacutainer tubes containing 3.2% citrate. For quality control, two separate TEG samples were taken and analyzed. The TEG analyses were performed by a single trained study nurse according to the manufacturer's guidelines. Citrated blood samples were stored at room temperature and analyzed within 30 min. The samples were recalcified before analyses. Kaolin was used as an initiator in each test. Two computerized TEG analyzers (TEG® 5000 Thromboelastograph® Hemostasis System, Haemonetics Corporation, Niles, USA) with four separate channels were used. The TEG analyzers were calibrated and tested regularly.

Data analysis and statistics

Summary statistics are presented as the mean with standard deviation (SD) or as the median with 25th and 75th percentiles unless otherwise stated. Repeated measures of TEG data were analyzed using linear mixed model (LMM), with patient as a random effect. Covariance pattern (i.e., correlation structure of the repeated measurements) was chosen according to Akaike's information criteria. If the LMM showed a $P_{time} < 0.05$ then time points were compared pairwise. Mean differences with 95% confidence intervals (CIs) are presented. Two-tailed p values are presented. Analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

A total of 54 blood samples were collected from 18 patients. Most patients were ASA II (55%) and female (83%). Hypertension and diabetes mellitus were the most common comorbidities (**Table 1**). All the patients underwent laparoscopic gastric bypass. There were no DVT or PE diagnosed during the follow-up. During the follow up period, the mean reduction in body weight was 19.5 kg (SD 6.8), and the mean reduction in BMI was 7.1 kg/m^2 (SD 2.6) (**Table 2**). All patients were still obese or overweight six months after the operation. None of the patients were lost during the six month follow-up.

Traditional laboratory tests

Before the operation, traditional coagulation tests were within the normal range (**Table 3**). HsCRP, which was elevated preoperatively in 10 (55 %) patients, increased significantly on the first postoperative day. There was a significant increase in D-dimer from baseline to the first postoperative day. During the follow up period, both values returned to baseline. Prior to the operation, fibrinogen level was elevated in eight patients (44%), yet the median fibrinogen level was within the normal range. The median fibrinogen concentration increased postoperatively, but the increase was not statistically significant. Subsequently, the median fibrinogen concentration remained elevated six months after the operation, however, there was no significant chance comparing to preoperative values (**Fig. 1**). At the follow-up, the fibrinogen level was above the normal value in 10 patients (55%).

TEG

The median R, K, α, and LY60 were within the normal ranges [18] during the whole study period (**Table 4**). However, the median MA and G were above the normal ranges and remained elevated up to the 6-month follow up (**Fig. 1**).

Discussion

To our knowledge, this is the first study assessing TEG parameters after weight loss following obesity surgery. We observed that the median MA and G, which indicate increased coagulation, remained elevated during the follow up. Our patients had increased median hsCRP preoperatively, with a further increase on the first postoperative day, followed by a decline to the normal range 6 months after the operation.

Obesity is associated in elevated risks of arterial and venous thrombosis, however; the underlying pathophysiological mechanism in only partly known [19]. Obesity causes prothrombotic changes in the coagulation system by increasing the levels of coagulation factors and decreasing the levels of fibrinolytic proteins [20]. Arterial thromboses, which result in cardiac ischemia or stroke, are usually a consequence of the rupture of an atherosclerotic plaque, while venous thromboses arise from venous stasis and hypercoagulation. Obesity-related metabolic syndrome is a well-established risk factor for cardiovascular events. Metabolic syndrome may also be a predisposing factor for VTE by inducing a procoagulant state, resulting in, for instance, elevated plasma levels of PAI-1; von Willebrandt factor (vWF); coagulation factors FVIII, FVII, FXIII; fibrinogen; and tissue factor (TF) [21]. However, even though metabolic syndrome seems to be related to VTEs, obesity itself predisposes to VTEs, with or without metabolic syndrome [22].

It is well-established that bariatric surgery and the weight loss that follows improves patients´ risk factors of cardiovascular events; yet, only a few studies have investigated the impact of bariatric surgery on blood coagulation. Gastric bypass improves patients´ hematological profile by normalizing, for example, T-Quick, AT III, fibrinogen, PAI-1 levels and endogenous thrombin potential (TG) [23-27]. Gastric bypass has demonstrated a greater impact on blood coagulation than sleeve gastrectomy [28]. However, both procedures improve fibrinolytic balance and normalize hemostatic variables and natural anticoagulants despite of antithrombin levels. In some cases, bariatric surgery may result in vitamin K deficiency and, furthermore, deficiencies in vitamin K-dependent clotting factors. The risk of vitamin K deficiency is greater in malabsorptive procedures, but may occur after restrictive procedures as well [28]. Many of the changes in blood coagulation, like changes in fibrinogen, FVIII, vWF and PAI-1 after bariatric surgery, are BMI-related [28]. Previous studies have shown improvements in the coagulation profile, even 1 month of the operation. ATIII and fibrinogen levels, for example, may not normalize until 12 months after surgery [23]. However, there is no data on whether this improvement in the coagulation profile reduces the risk of VTEs.

Only a few studies have investigated TEG [3,4,17] and ROTEM [29,30] parameters during bariatric surgery. These methods enable an assessment the viscoelastic properties of blood from the initiation of the coagulation cascade to fibrinolysis. TEG and ROTEM use whole blood to analyze the coagulation profile, whereas traditional coagulation tests are performed on plasma. The disadvantage of using plasma is that it does not take into account interactions between plasma and other blood components in the coagulation process. Furthermore, viscoelastic tests produce more precise information about clot stability and fibrinolysis. In these studies, patients have been shown to be hypercoagulative at the time of the operation as demonstrated by elevated MA and G, which are related to enhanced clot formation [3,4]. In comparison with patients of normal weight, patients who are morbidly obese also have reduced R and K, referring to enhanced initiation, as well as increased α, suggesting enhanced clot formation. However, R, K, and α vary within the normal range [17]. Earlier studies have also demonstrated a relationship between high fibrinogen levels and elevated G and MA values in TEG analyses of morbidly obese patients [4,17]. In our study, patients had elevated G and MA values preoperatively, and these values remained elevated until the end of the 6-month follow up. Fibrinogen levels were elevated in 45% of patients prior to the operation and in 65% of patients during the follow-up.

Ongoing inflammation is likely to be associated with a hypercoagulative state in patients with obesity [9], and may elevate the risk of VTE and myocardial infarctation (MI) [31]; yet, the association between inflammation and coagulation is unclear [32]. Previous research showed that hsCRP, which is a marker of inflammation, is elevated in patients who are obese [33]. In another study, hsCRP was normalized 12 months after gastric bypass as well as the traditional coagulation assays [24]. In our patient population, we observed a preoperative elevation of the median hsCRP, with a further increase on the first postoperative day, followed by a decline to the normal range 6 months after the operation. Our results are in agreements with earlier findings.

After bariatric surgery, the risk of DVT varies from 0.07% to 2.4% [34-38]. We observed no DVT or PE complications. Apart from BMI, age, and comorbidities, the type of bariatric procedure as well as the complexity and duration of surgery all have an impact on the risk [34,35,38]. In the present study, only two patients were superobese, and all were less than 61 years of age. Nine patients had none or only one comorbidity, and other patients had comorbidities that were well managed. All of our patients underwent a laparoscopic gastric bypass. All procedures were primary operations and the duration of the surgery was less than 100 min. When considering these special risk factors, the total risk of thromboembolic events in our patient population was only moderate, although TEG values were compliant with hypercoagulation.

Taken together, our findings support the idea that obesity-related proinflammatory activity is reduced following weight loss after surgery for obesity, although in our series patients remained hypercoagulative (elevated MA, G and fibrinogen). One explanation for a sustained hypercoagulative state in our series could be that our patients were still overweight or obese despite a mean decrease in BMI of 7.1 kg/m2. Since the duration of the follow-up was only 6 months, we can only speculate whether a longer follow-up period, enabling greater weight loss, might have resulted in favorable changes in these parameters.

Limitations

Our study has some limitations. The study population of only 18 patients was rather small and the patient population was rather heterogeneous. Since this was an observational pilot study we did not perform formal sample size calculation. According to the present results to observe normalization of MA value (MA upper normal value of 69 mm) after gastric bypass would have required 214 patients with a 80 % power and alpha of 0.05. However, our results showing hypercoagulation with TEG values are in line with changes in fibrinogen levels and also supported by earlier literature. Six months of follow up may be too early to see changes in coagulation. The patients lost more than 19 kg of their weight, but they were still obese at the end of the follow-up. An alternative would be to examine the data one year after surgery.

The repertoire of traditional coagulation tests was concise since we utilized laboratory tests that are commonly available and in clinical use. All our patients received a single dose of enoxaparine before T2 measurements. The anti-factor Xa (anti-fXA) was determined to examine the possible effect of enoxaparine on our results. According to low anti-fXA levels, the changes in hemostatic parameters on the first postoperative day cannot be explained by an enoxaparine effect.

Future studies

A longer follow up (12-24 months) is needed to evaluate whether the abnormalities in TEG parameters are normalized after greater weight loss following surgery for obesity.

Conclusions

Measured by TEG, bariatric patients have hemostatic abnormalities indicating hypercoagulation up to the 6-month follow-up period, suggesting an elevated risk for thromboembolic events for at least six months after surgery.

Conflict of interests

The authors have no conflict of interests.

Ethical approval statement

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Statement

Informed consent was obtained from all individual participants included in the study.

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Figure Legends

Table 1. Patient characteristics.

Table 2. The results and the description of the surgery.

Table 3. Median values with 25^{th} and 75^{th} percentiles of conventional laboratory test parameters during study period.

Table 4. Median values with 25^{th} and 75^{th} percentiles of thromboelastography parameters during study period.

Figure 1. Median values with 25^{th} and 75^{th} percentiles for fibrinogen, hsCRP, MA, and G preoperatively, on the first postoperative day and after six months follow up. hsCRP = high-sensitivity C-reactive protein, MA = maximum amplitude, G = clot strength. P_{time} indicates statistical significance for the change over whole study period.

	Total n=18
Age mean (SD) [min-max]	**48.17** years (9.9) [30-61]
ASA classification, n	
1	**1 (6%)**
2	**10 (55%)**
3	**7 (39%)**
Gender, n	
Female	**15 (83%)**
Male	**3 (17%)**
Comorbidities, n	
HTA	**10 (55%)**
T2DM	**7 (39%)**
Sleep apnea	**4 (22%)**
Asthma	**4 (22%)**
Hypothyreosis	**2 (11%)**
Fatty liver	**2 (11%)**
MS	**1 (6%)**
Pseudotumor cerebri	**1 (6%)**
None	**3 (17%)**
Smoking, n	
Yes	**2 (11%)**
No	**16 (89%)**

ASA, American Society of Anesthesiologists; T2DM, diabetes; HTA,hypertension ; MS, multiple sclerosis; SD, standard deviation.

	Total n=18
Height mean (SD) [min-max]	**166.2 cm** (6.7) [152-182]
BMI mean (SD) [min-max]	
Before (SD) [min-max]	**42.4** (5.8) [34.3-54.0]
After (SD) [min-max]	**35.0** (5.0) [27.3-44.8]
Obesity classes before operation, n	
Overweight	**0**
Obese	**2 (11%)**
Severe obese	**5 (28%)**
Morbidly obese	**9 (50%)**
Super obese	**2 (11%)**
Missing	**0**
Obesity classes 6 months after operation, n	
Overweight	**3 (17%)**
Obese	**5 (28%)**
Severe obese	**5 (28%)**
Morbid obese	**3 (17%)**
Super obese	**0**
Missing	**2 (11%)**
Change of BMI mean (SD) [95% CI]	**−7.1** (2.6) [5.7-8.5]
Weight mean	
Before (SD) [min-max]	**117.1 kg** (15.9) [96.4-147]
After (SD) [min-max]	**97 kg** (14.4) [78-125]
Change of weight mean (SD) [95% CI]	**−19.5 kg** (6.8) [15.8-23.1]
Type of surgery	
LRYGB	**18**
Duration of surgery mean, min (SD) [min-max]	**89.4 min** (17.0) [69-122]

SD, standard deviation; BMI, body mass index; CI = 95% confidence interval; LRYGB, laparoscopic Roux-en-Y gastric bypass.

	PREOP T1	POD 1 T2	6-month FU T3	P_{time}[a]	Normal range
	Median [25th-75th pct]	**Median** [25th-75th pct]	**Median** [25th-75th pct]		
Hb	**138.0** [134-148]	**130.5** [126-139]	**137.0** [125-141]	**<0.001**	**F** 117-155g/l **M** 134-167g/l
Platelets	**248.0** [197-287]	**239.5** [200-277]	**267.0** [221-319]	**0.038**	150-400 x 10^9
TT	**92.0** [87-102]	**74.5** [68-81]	**88.5** [83-93]	**<0.001**	70-130 %
INR	**1.0** [1.0-1.1]	**1.2** [1.1-1.2]	**1.1** [1.1-1.1]	**<0.001**	0.7-1.2
Fibrinogen	**3.75** [3.4-4.5]	**4.15** [3.7-4.5]	**4.05** [3.5-4.4]	0.19	2-4 g/l
D-dimer	**0.35** [0.3-0.6]	**0.75** [0.4-1.1]	**0.4** [0.2-0.8]	**0.007**	< 0.05 mg/l
hs-CRP	**3.5** [1.6-7.1]	19.6 [14.2-20.8]	1.15 [1-4]	**< 0.001**	**F** 0.05-3mg/l **M** 0.05-2.5mg/l

FU, follow up; Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; INR, International Normalized Ratio; pct, percentiles; POD, post-operative day; PREOP, preoperative; F, female; M, male.

[a] P-value according to linear mixed model.

	PREOP **T1**	**POD 1** **T2**	**6-month FU** **T3**	P_{time}[a]	**Normal range**
	Median [25th-75th pct]	**Median** [25th-75th pct]	**Median** [25th-75th pct]		
R	**7.5** [6.8-8]	**7.7** [7.2-8.6]	**7.7** [6.3-8.5]	0.5657	2-8 min
K	**1.5** [1.4-1.8]	**1.5** [1.4-1.8]	**1.5** [1.2-1.6]	0.3395	1-3 min
α	**68.3** [65.2-70.2]	**67.6** [65.5-70.2]	**68.8** [66.9-71.6]	0.2156	55-78°
MA	**71.3** [68-73]	**70.9** [67.7-72.6]	**70.4** [68.2-72.3]	0.7329	51-69 mm
G	**12403.3** [10647.9-13545.3]	**12179.0** [10466.4-13244]	**11847.6** [10717.1-13058.7]	0.7467	4600-10900 d/sc
LY60	**3.8** [2.4-5.8]	**3.7** [2.6-5.1]	**5.8** [3.7-7]	0.3385	0-15 %

α, angle; FU, follow up; G, clot strength; K, kinetics time; LY60, lysis at 60 minutes; MA, maximum amplitude; pct, percentiles; POD, post-operative day; PREOP, preoperative; R, reaction time

[a] P-value according to linear mixed model.