

# Effects of Obesity Surgery on Blood Coagulation and Fibrinolysis: A Literature Review

Else Marie Bladbjerg<sup>1,2</sup> Charlotte Røn Stolberg<sup>2,3</sup> Claus Bogh Juhl<sup>2,3</sup>

<sup>1</sup> Department of Clinical Biochemistry, Unit for Thrombosis Research, University Hospital of Southern Denmark, Esbjerg, Denmark

<sup>2</sup> Institute of Regional Health Research, University of Southern Denmark, Denmark

<sup>3</sup> Department of Medicine, Section of Endocrinology, University Hospital of Southern Denmark, Esbjerg, Denmark

**Address for correspondence** Else Marie Bladbjerg, MSc, PhD, Department of Clinical Biochemistry, Unit for Thrombosis Research, University Hospital of Southern Denmark, Institute of Regional Health Research, University of Southern Denmark, Finsensgade 35, 6700 Esbjerg, Denmark (e-mail: ebladbjerg@health.sdu.dk).

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## Abstract

**Objective** Obesity is characterized by a disturbed hemostatic balance with increased coagulation and impaired fibrinolysis. This increases the risk of thrombosis, and the risk is lowered after obesity surgery. Over the past 25 years, several studies have contributed to understand the mechanisms behind the antithrombotic effect of obesity surgery, and this literature review summarizes the results of these studies.

**Methods** A detailed literature search on the effects of obesity surgery on the hemostatic balance was conducted.

**Results** The 25 relevant studies reviewed demonstrated that obesity surgery has favorable effects on many biomarkers of coagulation and fibrinolysis. The evidence is substantial for fibrinogen and plasminogen activator inhibitor type 1 with average reductions from 1 to 24 months after obesity surgery of 17 and 48%, respectively. For most other biomarkers, the evidence is moderate or weak with average effect sizes varying from 2% for fiber mass length ratio to 70% for prothrombin fragment 1 + 2 and with a large variation between studies. Many studies are small and of short duration, and the surgical techniques differ. Also, studies are confounded by changes in medication, comorbidity, diet, and exercise. It is unknown whether the hemostatic changes are mediated by weight loss alone or by the accompanying metabolic improvements.

**Conclusion** Despite issues of confounding, this review suggests that obesity surgery shifts the hemostatic balance in the antithrombotic direction, thereby reducing the thrombotic potential of people with obesity, but more studies are needed for most of the biomarkers.

## Keywords

- bariatric surgery
- clot structure
- hemostasis
- obesity

## Introduction

The prevalence of obesity continues to increase worldwide,<sup>1</sup> and in 2015, a total of 100 million children and 600 million adults suffered from obesity.<sup>2</sup> The health consequences of obesity are enormous, and numerous studies have shown that obesity increases the risk of cardiovascular diseases (CVD),<sup>3–6</sup> a major

cause of morbidity and mortality. Surgical weight loss reduces the risk of CVD events and deaths,<sup>7,8</sup> suggesting causality between obesity and CVD. It is therefore highly important to understand the mechanisms linking obesity to CVD.

CVD is caused by atherosclerosis and thrombosis (atherothrombosis), that is, rupture of atherosclerotic plaques in the

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blood vessels leading to a disturbed hemostatic balance with increased fibrin clot formation.<sup>9,10</sup> It is well known that obesity has a negative impact on atherosclerosis as well as thrombosis. The effect of obesity on atherosclerosis involves chronic inflammation, hyperlipidemia, and endothelial dysfunction with the formation of foam cells and atherosclerotic plaques leading to narrowing of the blood vessels.<sup>11,12</sup> The effect of obesity on thrombosis is due to a disturbed hemostatic balance leading to procoagulant and hypofibrinolytic states with increased fibrin clot formation. In recent years, several studies have contributed to increase the understanding of how obesity pathophysiologically leads to a prothrombotic condition, as reviewed elsewhere.<sup>13–18</sup>

Obesity surgery is increasingly used as a treatment strategy for obesity, recognizing that lifestyle interventions only result in a modest weight loss without sustained long-term effects<sup>19</sup> whereas obesity surgery leads to a substantial weight loss<sup>7</sup> and reduces long-term mortality.<sup>8,20</sup> We and others have demonstrated that obesity surgery beneficially affects markers of atherosclerosis,<sup>21–23</sup> and several studies within the past 25 years have focused on the mechanisms behind the anti-thrombotic effect of obesity surgery. This literature review summarizes the results of these studies showing that obesity surgery shifts the hemostatic balance in the antithrombotic direction, thereby reducing the thrombotic potential.

## Obesity and Thrombosis

### The Hemostatic Balance

The risk of thrombosis is increased when the hemostatic balance is disturbed in the direction of a procoagulant state. The hemostatic balance was introduced more than 60 years ago<sup>24</sup> and is a cascade of enzymatic activators and inhibitors responsible for regulating the equilibrium between blood coagulation with tissue repair at the vascular surface and fibrinolysis with clot dissolution. Hemostasis also involves platelets, but platelet migration and activation are not part of this review in which the hemostatic balance defines the balance between coagulation and fibrinolysis. A simplified overview of coagulation and fibrinolysis is presented in ► Fig. 1.

The physiologically most important activator of blood coagulation is tissue factor (TF), a transmembrane glycoprotein present in subendothelial tissue, in monocytes, and on circulating blood cell microvesicles.<sup>25</sup> When TF is exposed to circulating blood, for example, after vessel wall injury or expression on monocytes/microvesicles, it activates the TF pathway of blood coagulation by acting as a receptor for factor VIIa (FVIIa). Activation of the clotting cascade leads to the generation of thrombin when the enzymatic inactive proenzyme prothrombin is activated by the prothrombinase complex, simultaneously cleaving off prothrombin fragment 1 + 2 (F1 + 2). Thus, F1 + 2 is a marker of endogenous thrombin generation (TG). Next, thrombin converts fibrinogen into fibrin polymers with the release of fibrinopeptides A and B (FP A and B). The fibrin polymers are cross-linked by activated factor XIII (FXIIIa) into an insoluble fibrin clot composed of a network of fibrin fibers.<sup>24,26,27</sup> The fibrin network serves as a matrix for reparative processes in the damaged endothelium. Because coagula-

tion activation is amplified by increasing amounts of thrombin (► Fig. 1), coagulation inhibitors such as tissue factor pathway inhibitor (TFPI), protein C, protein S, and antithrombin (AT) are highly important regulators of the hemostatic balance. Also, fibrinolytic enzymes are responsible for tipping the hemostatic balance in the direction of anticoagulation, and the most important fibrinolytic activator is the endothelial-derived protein tissue plasminogen activator (t-PA). This enzyme activates plasminogen into the enzymatic active form plasmin on the fibrin clot surface leading to plasmin-induced degradation of fibrin (fibrinolysis) into soluble fibrin degradation products, for example, D-dimer. In blood, t-PA is inhibited by the plasminogen activator inhibitor type 1 (PAI-1), and high concentrations of PAI-1, therefore, impair fibrin clearance.<sup>24,26,27</sup> Likewise, fibrinolysis is inhibited by plasmin inhibitor (PI or  $\alpha_2$ -anti-plasmin), which inactivates plasmin, and thrombin activatable fibrinolysis inhibitor (TAFI) that protects the clot against lysis by destroying the binding sites for plasminogen.<sup>26</sup>

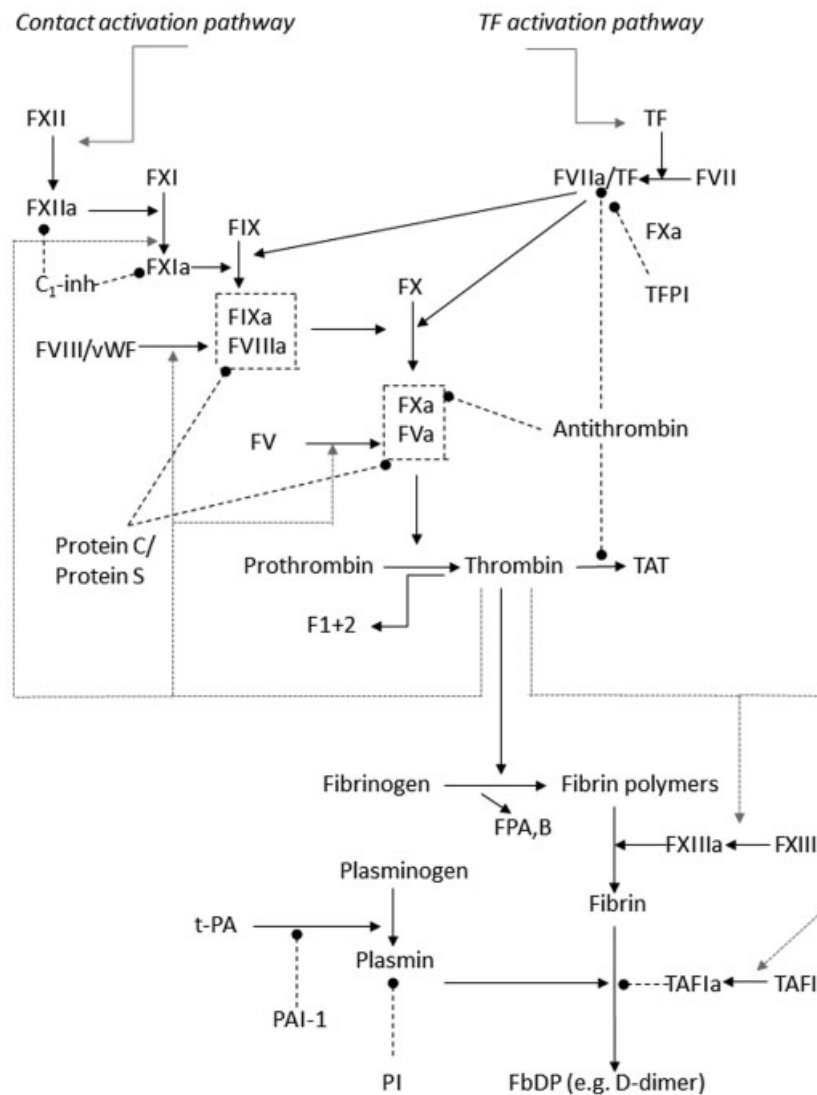
### Obesity: a Proinflammatory State

Obesity is characterized by excessive amounts of visceral and subcutaneous adipose tissue infiltrated with proinflammatory cells such as macrophages.<sup>28</sup> Obesity is defined at a body mass index (BMI) above 30 kg/m<sup>2</sup>, and BMI can be further divided into obesity of class I (BMI: 30–34.9 kg/m<sup>2</sup>), class II (BMI: 35–39.9 kg/m<sup>2</sup>), and class III (BMI > 40 kg/m<sup>2</sup>). Adipose tissue contributes to the systemic chronic low-grade inflammation observed in obesity as reviewed in detail elsewhere.<sup>29,30</sup> In brief, adipose tissue is an endocrine organ that secretes a high number of proinflammatory cytokines (adipokines), for example, interleukin 6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and hormones such as leptin. Among these, IL-6 is a central player known to stimulate the production of the inflammatory acute phase protein, C-reactive protein (CRP), in the liver. Further, adipose tissue releases monocyte chemoattractant protein 1 (MCP-1) which attracts immune cells such as macrophages, thereby further increasing the production of inflammatory cytokines.<sup>31–33</sup>

### Obesity and the Hemostatic Balance

The association between obesity and biomarkers of the hemostatic balance has been the focus for several reviews.<sup>13–18</sup> Put together, the proinflammatory cytokines in adipose tissue contribute to tip the hemostatic balance toward a prothrombotic state. Thus, IL-6, TNF $\alpha$ , and leptin play key roles by stimulating the endothelial synthesis of the procoagulant protein TF and the fibrinolytic inhibitor PAI-1. Further, IL-6, TNF $\alpha$ , and leptin increase TF-expression from circulating monocytes<sup>34–36</sup> resulting in elevated levels of TF-bearing microvesicles in blood.<sup>37</sup> The proinflammatory cytokines also stimulate the hepatic production of coagulation factors, e.g., fibrinogen, FVII, and FVIII<sup>17</sup> and the fibrinolytic inhibitor PAI-1<sup>38,39</sup> and induce platelet activation with increased production of PAI-1.<sup>14</sup> Additionally, the blood concentrations of PAI-1 and TF in obesity are further elevated due to enhanced synthesis of these proteins in adipose tissue.<sup>38,40,41</sup>

In line with this, several studies have compared a number of hemostatic biomarkers in people with obesity and normal



**Fig. 1** Overview of coagulation and fibrinolysis. The subscript "a" denotes activated enzymes. Solid lines indicate activation, dashed black lines inhibition, and dashed gray lines indicate thrombin activation. Several activation steps require calcium, and also phospholipids are needed for normal enzymatic function of the tenase (FIXa and FVIIIa) and prothrombinase (FXa and FVa) complexes. C1-inh, C1-inhibitor; F, coagulation factor (e.g., FVII); FbDP, fibrin degradation product; PAI-1, plasminogen activator inhibitor type 1; PI, plasmin inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TAT, thrombin-antithrombin complexes; F1 + 2, prothrombin fragment 1 + 2; FPA,B, fibrinopeptide A or B; TAFI, thrombin activatable fibrinolysis inhibitor; t-PA, tissue plasminogen activator.

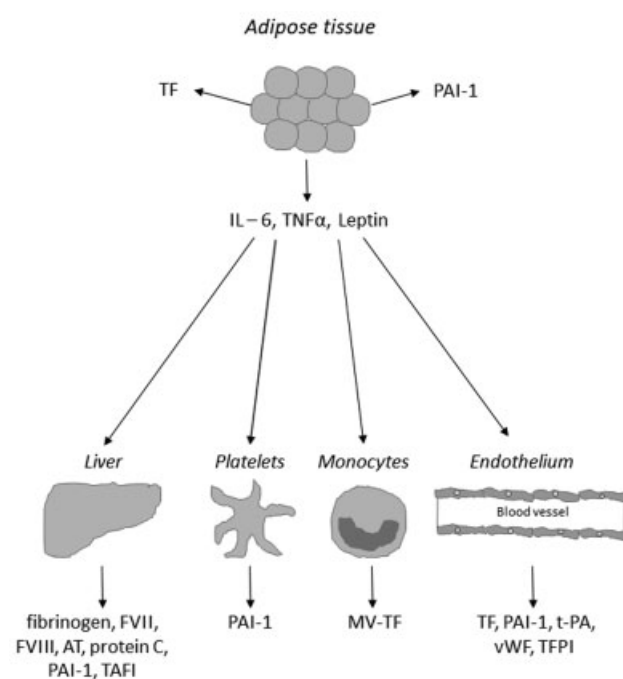
weight. These studies conclude that obesity is accompanied by increased levels of biomarkers of endothelial function, e.g., t-PA:Ag and von Willebrand factor (vWF),<sup>42–46</sup> coagulation, e.g., fibrinogen, FVII, TF, factor IX (FIX), factor X (FX), factor XII (FXII), F1 + 2, thrombin-AT complexes (TAT), D-dimer,<sup>34,42,44,45,47–52</sup> and impaired fibrinolysis, for example, PAI-1<sup>42,43,45,46,51,53</sup> and TAFI.<sup>54,55</sup> Interestingly, it has been suggested that obesity is accompanied by elevated concentrations of coagulation inhibitors, such as protein C, AT, and TFPI,<sup>38,52,56</sup> perhaps as a protective response toward the increased thrombotic risk in obesity. However, the net effect is an increased endogenous thrombin generation potential (ETP),<sup>48,57,58</sup> and also hypercoagulable and hypofibrinolytic states have been identified in whole blood thromboelastography (TEG).<sup>59</sup>

In summary, the consequences of obesity are chronic low-grade inflammation causing endothelial dysfunction, plate-

let activation, hypercoagulability, and impaired fibrinolysis (→Fig. 2). This shifts the hemostatic balance in the prothrombotic direction, thereby increasing the thrombotic risk. In particular, TF and PAI-1 are central contributors to the prothrombotic state by serving as activator of the TF pathway of blood coagulation and inhibitor of fibrinolysis, respectively (→Fig. 1).

## Obesity Surgery

Surgical procedures for the treatment of obesity were introduced as early as 1952.<sup>60</sup> In the following years, a multitude of surgical procedures were introduced; many of which carried the risk of treatment failure, high mortality rates, and unacceptable complications. Historically, the surgical procedures have been categorized according to their presumed mechanisms of action. Thus, restrictive procedures



**Fig. 2** Hemostatic consequences of low-grade inflammation in obesity. AT, antithrombin; FVII, coagulation factor VII, FVIII, coagulation factor VIII; IL-6, interleukin-6; MV-TF, microvesicle tissue factor; PAI-1, plasminogen activator inhibitor type 1; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; t-PA, tissue plasminogen activator; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

such as gastric stapling, sleeve gastrectomy (SG), and gastric banding (GB) reduce food intake, while malabsorptive procedures such as Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion, and duodenal switch work primarily by introducing a “controlled malabsorption.” During recent years, the surgical procedures have been proven to increase the release of gut hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), and accumulating evidence shows that gut hormones are major players in the effect of various procedures on both glucose homeostasis and weight loss.<sup>61</sup> Today, the preferred procedures are RYGB and SG. No valid data on the global number of surgeries are available, but a global registry report from 2018 contains almost 400,000 cases.<sup>62</sup>

## Obesity Surgery and the Hemostatic Balance

### Literature Search

A detailed literature search on the effects of obesity surgery on the hemostatic balance was conducted on the PubMed database. The search was structured in two parts. In part 1, literature on the hemostatic balance was found using the following query: “hemostasis” (MeSH) OR “blood coagulation” (MeSH) OR “fibrinolysis” (MeSH) OR “fibrin” (MeSH) OR “hemostasis” OR “blood coagulation” OR “fibrinolysis” OR “fibrin.” This resulted in 211,535 papers. In part 2, literature on obesity surgery was found using the following query: “bariatric surgery” (MeSH) OR “bariatric surgery” OR “gastric sleeve” OR “sleeve gastrectomy.” This resulted in 31,166 papers. Next, part

1 and part 2 were combined with the operator AND which resulted in 232 papers. Studies were only considered relevant for this review when they were published in English and conducted in humans leaving 194 relevant papers. The search was repeated on the Embase database, but no additional relevant studies were included. All papers were thoroughly investigated, and the reference lists were assessed for relevant papers to include in the review. Finally, 25 papers were selected based on the following criteria:

### Inclusion Criteria

Coagulation and fibrinolysis biomarkers measured in blood before and after obesity surgery.

### Exclusion Criteria

Studies including postsurgery measurements only in the first months after surgery.

The search was updated on November 18, 2019, and a detailed search strategy is presented in ►Fig. 3.

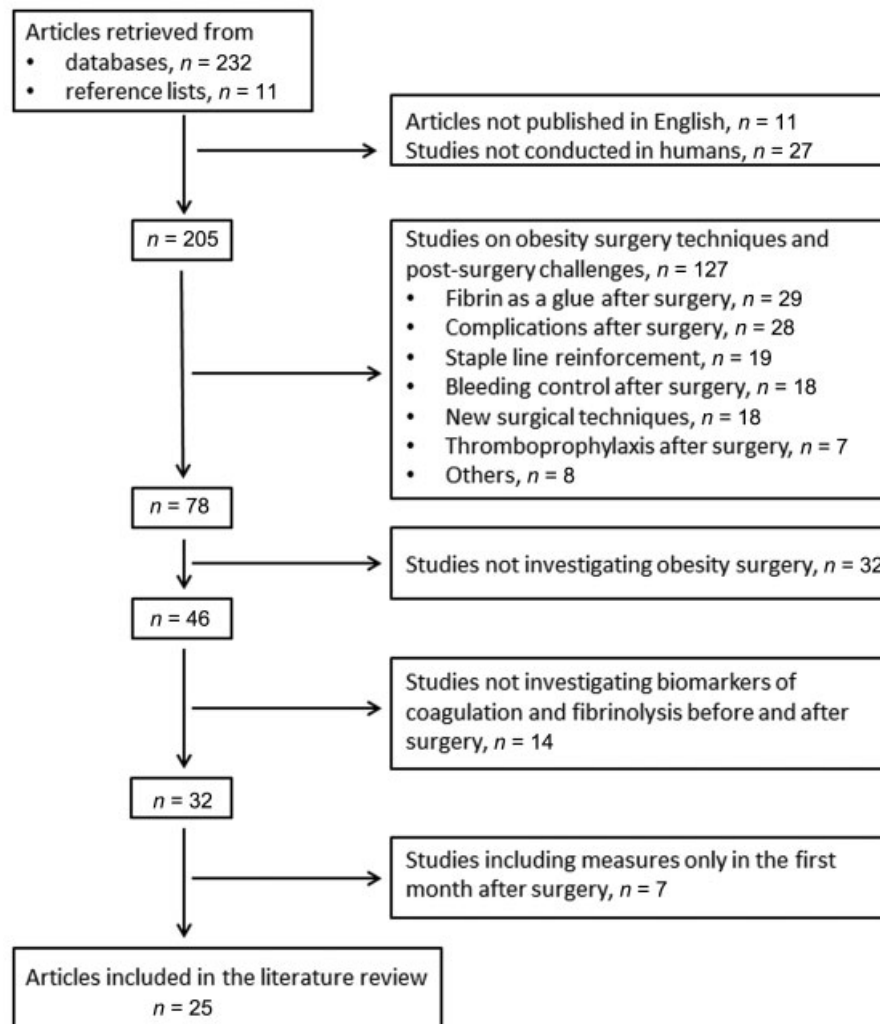
### Findings from the Literature

Relevant studies are summarized in ►Table 1 with respect to surgical procedures, study participants, time of blood sampling, measured biomarkers, and main results. Studies conducted in the period from 1992 to 2009 mainly used various modifications of GB as surgical technique. Later, RYGB became the preferred procedure until SG was introduced, and studies conducted since 2015 mainly used RYGB or SG. The study participants fulfilled the criteria for obesity surgery, and the mean BMI varied from 42 to 54 kg/m<sup>2</sup>. The average age was 35 to 52 years, and most of the patients were women.

In all studies, venous blood samples were obtained before surgery (baseline), whereas postsurgery sampling included various time points between 1 and 24 months (►Table 1). Blood samples were analyzed for a high number of hemostatic biomarkers, and the results are summarized in ►Table 2 with average effect sizes calculated for variables that change significantly after surgery.

### Obesity Surgery and Coagulation

Overall, obesity surgery favorably affects several biomarkers of coagulation, thereby reducing the hypercoagulable state associated with obesity. As outlined in ►Fig. 2, a reduction in fat mass is accompanied by decreased levels of pro-inflammatory cytokines<sup>63</sup> and consequently, a decreased synthesis of several hemostatic biomarkers. In the TF pathway of coagulation, MV-TF, monocyte-TF, and TF:Ag were lowered 2 to 24 months after vertical gastroplasty,<sup>64</sup> SG,<sup>65</sup> RYGB, or GB.<sup>57,66,67</sup> This may be explained by decreased TF-synthesis from adipose tissue, endothelial cells, and monocytes (►Fig. 2). Further, concentrations of liver-derived proteins are reduced, thereby reducing FVII activity 3 to 12 months after gastric stapling or banding,<sup>45,68</sup> FVII:Ag 14 months after vertical gastroplasty,<sup>64</sup> and fibrinogen 1 to 24 months after vertical gastroplasty, GB, RYGB, or SG.<sup>38,45,64,68–72</sup> Only two out of many studies did not find an effect on fibrinogen, that is, 1 month after RYGB ( $n = 45$ ) or SG ( $n = 57$ )<sup>73</sup> and 6 months after RYGB ( $n = 18$ )<sup>74</sup> and after an average weight loss of only 12 to 16%. The FVIII activity



**Fig. 3** QUORUM flow chart presenting the literature search strategy.

was not affected 12 months after gastric stapling, RYGB, or SG.<sup>68,71</sup> Also, the vitamin K dependent coagulation inhibitors protein C and protein S are synthesized by the liver. One of the first studies of obesity surgery and hemostasis by Primrose et al measured protein C antigen 6 and 12 months after vertical gastric stapling in 19 patients. Protein C was measured with the old “rocket” immuno electrophoresis method, and no significant change was observed despite an average weight loss of 42% after 12 months.<sup>68</sup> Another study measured protein C activity and protein S antigen 2 months after RYGB or SG and reported significantly lower concentrations after RYGB than after SG. However, potential within-group effects (RYGB and SG, respectively) were not analyzed.<sup>75</sup> Opposite to other liver-derived proteins, studies have reported an increase<sup>38,70</sup> or no change<sup>68</sup> in AT 6 and 12 months after obesity surgery. An increase in AT might indicate a long-term postsurgical protective anticoagulant effect, but further studies are needed since ethylenediaminetetraacetic acid (EDTA)-plasma, and not citrated plasma as recommended for the anti-FXa assay, was used in the studies by Pardina et al<sup>38</sup> and Ferrer et al,<sup>70</sup> two studies from the same bariatric cohort presenting the same AT results in two different ways.

A reduction in fat mass is also expected to lower concentrations of endothelial-derived proteins (► **Fig. 2**). In line with this, concentrations of vWF (vWF:Ag), a glycoprotein binding to FVIII in blood, was lowered 3 to 24 months after GB or RYGB<sup>22,45,46</sup> when measured with an ELISA, whereas no effect was reported 6 to 12 months after surgery when vWF was analyzed by “rocket” immuno electrophoresis (after vertical gastric stapling)<sup>68</sup> or the STA-R Evolution Analyzer (after RYGB or SG).<sup>71</sup> Besides methodological differences, there are no obvious explanations for these conflicting results for vWF. Conflicting results were also reported for TFPI, an important inhibitor of the TF pathway of coagulation and also synthesized by endothelial cells. Thus, 14 months after vertical gastroplasty, total TFPI and free TFPI were reduced,<sup>64</sup> whereas no effect was observed for total TFPI 24 months after RYGB or GB.<sup>57</sup> The two studies were from the same research group, the same Imubind TFPI ELISA was used and weight loss was almost the same, but the surgical procedures and postsurgery follow-up time were different.

The marker of *in vivo* thrombin formation, F1 + 2, has been assessed in only three studies, and all three studies used the Enzygnost ELISA. However, presurgery values were



**Table 1** Summary of studies in the literature review

Author (year)	Surgical procedures	Patients	Blood samples	Hemostatic biomarkers	Main results
Primrose et al <sup>68</sup> (1992)	Vertical gastric stapling (n = 11) + limited jejuno-ileal bypass (n = 8)	13 W, 6 M Age: 36 years BW: 154 kg	0, 6, and 12 months	FVIIc, fibg, euglobulin clot lysis, tPA act, PAI act, vWF:Ag, FVIIIc, α <sub>2</sub> -AP, PC: Ag, AT, FPA	6 and 12 months: ↓ BMI, FVIIc, fibg, euglobulin clot lysis, tPA act, PAI act
Kopp et al <sup>64</sup> (2003)	Vertical gastropasty	33 W, 4 M Age: 41 years BW: 136 kg BMI: 49 kg/m <sup>2</sup>	0 and 14 months	PT, TF:Ag, TFPI:Ag, free TFPI, FVII:Ag, F1 + 2, fibg	↓ BMI, PT, TF:Ag, TFPI:Ag, free TFPI, FVII:Ag, F1 + 2, fibg
Uzun et al <sup>79</sup> (2004)	Open (n = 20, group 1) and laparoscopic (n = 20, group 2) GB	Group 1: 10 W, 10 M Age: 35 years BW: 145 kg BMI: 54 kg/m <sup>2</sup> Group 2: 11 W, 9 M Age: 35 years BW: 157 kg BMI: 53 kg/m <sup>2</sup>	0 and 6 months	PAI:Ag	↓ BMI and PAI:Ag. No difference between the two surgical procedures
Van Dielen et al <sup>80</sup> (2004)	Vertical banded gastropasty (n = 11), laparoscopic GB (n = 15), and gastric bypass (n = 1)	22 W, 5 M Age: 38 years BMI: 47 kg/m <sup>2</sup>	0, 3, 6, 12, and 24 months	PAI:Ag	↓ BMI and PAI:Ag at all time points
Vázquez et al <sup>46</sup> (2005)	Vertical-banded gastropasty (n = 18), bilio-pancreatic diversion (n = 8)	23 W, 3 M Age: 39 years BW: 126 kg BMI: 46 kg/m <sup>2</sup>	0 and 4 months	PAI:Ag, vWF:Ag	↓ BMI, PAI:Ag, vWF:Ag
Hanusch-Enserer et al <sup>81</sup> (2009)	GB	29 W, 3 M Age: 42 years BW: 130 kg BMI: 46 kg/m <sup>2</sup>	0, 6, and 12 months	PAI:Ag	↓ BMI and PAI:Ag at both time points
Ay et al <sup>57</sup> (2010)	RYGB (n = 26) or GB (n = 10)	29 W, 7 M Age: 42 years BW: 130 kg BMI: 45 kg/m <sup>2</sup>	0 and 24 months	TF:Ag, TFPI:Ag, F1 + 2, TG, PAI:Ag	↓ BMI, TF:Ag, F1 + 2, peak thrombin, PAI:Ag ↑ lag phase
Brethauer et al <sup>69</sup> (2011)	RYGB	11 W, 4 M Age: 49 years BMI: 49 kg/m <sup>2</sup>	0, 3, and 6 months	Fibg and PAI:Ag	↓ BMI, fibg (3 months), PAI:Ag (3 and 6 months)
Cugno et al (2012) <sup>45</sup>	GB	25 W Age: 40 years BMI: 43 kg/m <sup>2</sup>	0, 3, 6, and 12 months	FVIIc, fibg, PAI act, vWF:Ag	↓ BMI, FVIIc, fibg, PAI, vWF, all time points
Tschoner et al <sup>82</sup> (2012)	GB (n = 29) or RYGB (n = 8)	28 W, 9 M Age: 35 years BW: 126 kg BMI: 42 kg/m <sup>2</sup>	0 and 18 months	PAI:Ag	↓ BMI and PAI:Ag. Different between the surgical procedures
Pardina et al <sup>38</sup> (2012)	RYGB	24 W, 10 M Age: 21–61 years BMI: 49 kg/m <sup>2</sup>	0, 1, 6, and 12 months	Fibg, AT, PAI:Ag, PAI mRNA from liver and adipose tissue	↓ BMI, fibg (12 months), PAI:Ag (3, 6, and 12 months) ↓ PAI mRNA from liver (6 months) and fat (6 and 12 months) ↑ AT (6 and 12 months)
Cheng et al <sup>89</sup> (2013)	RYGB (n = 9) or gastric restrictive surgery (n = 5)	7 W, 7 M Age: 52 years BMI: 47 kg/m <sup>2</sup>	0, 1, and 12 months	MV-TF (flowcytometry)	↓ BMI ↓ MV-TF (p = 0.1)
Dawson et al <sup>86</sup> (2014)	RYGB	9 patients BW: 133 kg BMI: 49 kg/m <sup>2</sup>	0 and 12 months	Clot structure and lysis	↓ BMI and clot lysis time
Ferrer et al <sup>70</sup> (2015)	RYGB	23 W, 9 M Age: 21–61 years BMI: 49 kg/m <sup>2</sup>	0, 1, 6, and 12 months	APTT, PT, fibg, AT, PAI:Ag	↓ BMI, fibg, PAI:Ag ↑ PT and AT
Minervino et al <sup>67</sup> (2015)	RYGB	31 W/M BMI: 46 kg/m <sup>2</sup>	0, 3, 6, and 12 months	MC-TF	↓ BMI and MC-TF
Netto et al <sup>83</sup> (2015)	RYGB	39 W, 2 M Age: 39 years BMI: 45 kg/m <sup>2</sup>	0 and 6 months	PAI total	↓ BMI and PAI

**Table 1** (Continued)

Author (year)	Surgical procedures	Patients	Blood samples	Hemostatic biomarkers	Main results
Lupoli et al <sup>75</sup> (2015)	RYGB ( <i>n</i> = 77) and SG ( <i>n</i> = 79)	RYGB: 32 W, 45 M Age: 39 years BMI: 44 kg/m <sup>2</sup> Sleeve: 43 W, 36 M Age: 38 years BMI: 45 kg/m <sup>2</sup>	0 and 2 months	FIIc, FVIIc, FVIIIc, FIXc, FXc, vWF:Ag, fibg, D-dimer, AT act, PC act, PS: Ag, PAI:Ag, tPA:Ag	↓ BMI FVIIc, FVIIIc, FIXc, vWF, fibg, D-dimer, PC act, PS: Ag, all lower after RYGB than sleeve
Ay et al <sup>66</sup> (2016)	RYGB ( <i>n</i> = 58) or GB ( <i>n</i> = 16)	61 W, 13 M Age: 41 years BW: 130 kg BMI: 46 kg/m <sup>2</sup>	0 and 12 months	MV-TF act, D-dimer, TG	↓ BMI, MV-TF, D-dimer, and peak thrombin
Campello et al <sup>65</sup> (2016)	SG	10 W, 10 M Age: 43 years BMI: 48 kg/m <sup>2</sup>	0, 3, and 12 months	MV-TF (flowcytometry)	↓ BMI and MV-TF
Thereaux et al <sup>71</sup> (2017)	RYGB ( <i>n</i> = 20) and SG ( <i>n</i> = 17)	27 W, 10 M Age: 44 years BW: 124 kg BMI: 45 kg/m <sup>2</sup>	0 and 12 months	TG (ETP, thrombin peak, time to peak, lag time at 1 and 20 pM TF), PT, APTT, fibg, FVIIIc, vWF:Ag, D-dimer, FbDP	↓ BMI, PT, fibg, ETP, thrombin peak Lag time (20 pM TF only)
Thereaux et al <sup>73</sup> (2017)	RYGB ( <i>n</i> = 45) and SG ( <i>n</i> = 57)	79 W, 23 M Age: 41 years BW: 126 kg BMI: 46 kg/m <sup>2</sup>	0 and 1 month	ETP and fibg	↓ BMI ↓ ETP ( <i>p</i> = 0.08)
Stolberg et al <sup>72</sup> (2018)	RYGB	42 W, 18 M Age: 42 years BW: 127 kg BMI: 43 kg/m <sup>2</sup>	0, 6, (24 months, <i>n</i> = 19)	TG (ETP, thrombin peak, time to peak, lag time at 5 pM TF), fibrin clot properties (clot lysis, clot formation Vmax, fiber diameter, mass-length ratio, diameter, density), F1 + 2, D-dimer, fibg, fibrinolytic activity, PAI:Ag	↓ BMI, ETP, thrombin peak, time to peak, lag time, Vmax, fiber diameter, fibg, PAI:Ag ↑ fiber density and clot lysis (after 24 months also ↓ D-dimer and ↑ fibrinolytic activity)
Stolberg et al <sup>22</sup> (2018)	RYGB	42 W, 18 M Age: 42 years BW: 127 kg BMI: 43 kg/m <sup>2</sup>	0 and 6 months (24 months, <i>n</i> = 19)	vWF:Ag and tPA:Ag	↓ BMI, vWF:Ag, tPA:Ag (after 24 months ↓ tPA:Ag)
Tuovila et al <sup>74</sup> (2018)	RYGB	15 W, 3 M Age: 48 years BW: 117 kg BMI: 42 kg/m <sup>2</sup>	0 and 6 months	Fibg, D-dimer, TEG (R, angle, MA, LY60, clot strength)	↓ BMI
Samuels et al <sup>59</sup> (2019)	SG ( <i>n</i> = 25) and RYGB ( <i>n</i> = 47)	65 W, 7 M Age: 41 years BMI: 45 kg/m <sup>2</sup>	0 and 6 months ( <i>n</i> = 36)	TEG (R, angle, MA, LY30, tPA-LY30). Proteomics (vitronectin and fibronectin)	↓ BMI, MA, vitronectin, fibronectin ↑ R, tPA-LY30

Abbreviations: APTT, activated partial thromboplastin time; AT act, antithrombin activity; BW, body weight; ETP, endogenous thrombin potential; F1 + 2, prothrombin fragment 1 + 2; FbDP, fibrin degradation products; Fibg, fibrinogen; FIIc, factor II coagulant activity; FIXc, factor IX coagulant activity; FPA, fibrinopeptide A; FVIIc or FVII:Ag, factor VII coagulant activity or antigen; FVIIIc, factor VIII coagulant activity; FXc, factor X coagulant activity; GB, gastric banding; LY30 and LY60, fibrinolysis 30 (and 60) minutes after max amplitude in TEG; M, men; MA, max amplitude; MC-TF, monocyte tissue factor; mo, months; MV-TF, microvesicle tissue factor; PAI act or PAI:Ag, plasminogen activator inhibitor type 1 activity or antigen; PC act or PC:Ag, protein C activity or antigen, PS:Ag, protein S antigen; PT, prothrombin time; R, reaction time; RYGB, Roux-En-Y gastric bypass; SG, sleeve gastrectomy; TEG, thromboelastography; TF:Ag, tissue factor antigen; TFPI:Ag, tissue factor pathway inhibitor antigen; TG, thrombin generation; tPA act or tPA:Ag, tissue plasminogen activator activity or antigen; tPA-LY30, fibrinolysis 30 minutes after max amplitude in TEG with addition of tPA; vWF:Ag, von Willebrand factor antigen; W, women; we, weeks;  $\alpha_2$ -AP,  $\alpha_2$ -antiplasmin.

highly different spanning from 190 pM<sup>72</sup> to 1,200 pM<sup>57</sup> and 2,400 pM<sup>64</sup> most likely reflecting a change in capture antibody from polyclonal to monoclonal for the Enzygnost ELISA over the years, but perhaps also reflecting problems with blood sampling in individuals with obesity leading to falsely increased F1 + 2 levels.<sup>76</sup> Two studies observed a F1 + 2 reduction 14 to 24 months after surgical-induced weight loss of 32%,<sup>57,64</sup> and one study observed no F1 + 2 change 6 months after a weight loss of 21%.<sup>72</sup> These conflicting findings might be due to weight loss differences.

The results from single-factor studies have been extended with observations from global coagulation assays in plasma.

The activated partial thromboplastin time (APTT), reflecting the contact activation pathway of coagulation was measured in two studies, and no APTT changes were observed 12 months after RYGB or SG.<sup>70,71</sup> Conflicting results were observed for prothrombin time (PT), reflecting the TF-pathway of coagulation, with a reported PT prolongation (measured in EDTA-plasma, which is not recommended) 12 months after RYGB<sup>70</sup> or a PT reduction 12 to 14 months after RYGB, SG,<sup>71</sup> or vertical gastroplasty.<sup>64</sup>

The TG test is an increasingly used method for assessment of the coagulation activation potential in plasma.<sup>77</sup> In this assay, citrated plasma is mixed with calcium, phospholipids, and TF,

**Table 2** Evidence for effects of obesity surgery on coagulation and fibrinolysis

Evidence	Hemostatic biomarker	Effect size <sup>a</sup>
Substantial evidence	↓ Fibg, <sup>38,45,64,68–72</sup> → Fibg <sup>73,74</sup>	17 (6–35)%
	↓ PAI:Ag <sup>38,46,57,69,70,72,79–83</sup>	48 (13–80)%
Moderate evidence	↓ ETP and ↓ thrombin peak <sup>57,66,71,72</sup> (TG)	ETP: 22 (19–28)%, thrombin peak: 25 (15–35)%
	↓ TF:Ag, <sup>57,64</sup> ↓ MV-TF, <sup>65,66</sup> ↓ MC-TF <sup>67</sup>	TF:Ag: 42 (25–59)%, MV-TF: 62 (33–90) %, MC-TF: 57%
Weak evidence	↓ FVIIc, <sup>45,68</sup> ↓ FVII:Ag <sup>64</sup>	FVIIc: 14 (12–16)%, FVII:Ag: 13%
	→ FVIII <sup>68,71</sup>	
	→ PC:Ag <sup>68</sup>	
	↑ AT act, <sup>38,70</sup> → AT <sup>68</sup>	8 (8–8)%
	↓ vWF:Ag, <sup>22,45,46</sup> → vWF:Ag <sup>68,71</sup>	12 (9–17)%
	↓ TFPI, total and free, <sup>64</sup> → total TFPI <sup>57</sup>	Total TFPI: 7%, free TFPI: 8%
	↓ F1 + 2, <sup>57,64</sup> → F1 + 2 <sup>72</sup>	70 (53–86)%
	→ APTT <sup>70,71</sup>	
	↑ PT, <sup>70</sup> ↓ PT <sup>64,71</sup>	14% (↑), 5 (4–5)% (↓)
	↓ time to peak, <sup>72</sup> → time to peak, <sup>71</sup> ↓ lag time, <sup>71,72</sup> ↑ lag time <sup>57</sup> (TG test)	Time to peak: 10%, lag time: 12 (10–14)%, lag time: 70%
	↑ R, ↓ MA, <sup>59</sup> → R, MA <sup>74</sup> (TEG)	R: 10%, MA: 3%
	↑ Fibrinolytic activity <sup>59,68,72</sup>	49 (18–69)%
	↓ PAI act, <sup>45,68</sup> ↓ PAI mRNA <sup>38</sup>	PAI act: 67 (63–70) %, PAI mRNA: 50%
	↓ t-PA:Ag <sup>22</sup>	23%
	↓ D-Dimer, <sup>66,72</sup> → D-Dimer <sup>71,72,74</sup>	13 (5–20)%
	→ α <sub>2</sub> -AP, → FPA <sup>68</sup>	
	↑ Clot lysis <sup>72,86</sup>	58 (46–69)%
	Clot structure (↓ Vmax, ↓ fiber mass-length ratio, ↓ fiber diameter, ↑ fiber density) <sup>72</sup>	Vmax: 7%, fiber mass-length ratio: 2%, fiber diameter: 7%, fiber density: 3%
No evidence	TAFI, FXIII, plasminogen, PI, clot permeability, contact activation (e.g., FXIIa)	

Abbreviations: APTT, activated partial thromboplastin time; ETP, endogenous thrombin potential; F1 + 2, prothrombin fragment 1 + 2; FbDP, fibrin degradation products; Fibg, fibrinogen; FPA, fibrinopeptide A; FVIIc or FVII:Ag, factor VII coagulant activity or antigen; FVIIIc, factor VIII coagulant activity; FXIIa, activated factor XII; FXIII, factor XIII; MA, max amplitude; MC-TF, monocyte tissue factor; MV-TF, microvesicle tissue factor; PAI act or PAI:Ag, plasminogen activator inhibitor type 1 activity or antigen; PC:Ag, protein C antigen; AT act, antithrombin activity; PI, plasmin inhibitor; PT, prothrombin time; R, reaction time; TAFI, thrombin activatable fibrinolysis inhibitor; TEG, thromboelastography; TF:Ag, tissue factor antigen; TFPI, tissue factor pathway inhibitor antigen; TG, thrombin generation; tPA act or tPA:Ag, tissue plasminogen activator activity or antigen; vWF:Ag, von Willebrand factor antigen; α<sub>2</sub>-AP, α<sub>2</sub>-antiplasmin.

↑, increased; ↓, reduced; →, unchanged.

<sup>a</sup>The unstandardized effect size was calculated as the relative change 1 to 24 months after surgery compared with presurgical values. Only significant changes were included in the reported mean (range) values.

and TG curves are generated to display lag time, time to peak, thrombin peak, and ETP. The assay has been applied in five studies,<sup>57,66,71–73</sup> and ETP and peak thrombin decreased 6, 12, and 24 months after RYGB, GB, or SG.<sup>57,66,71,72</sup> The time until peak thrombin formation (time to peak) was reduced 6 and 24 months after RYGB,<sup>72</sup> but not 12 months after RYGB or SG.<sup>71</sup> The time it takes until the first amounts of thrombin are generated (lag time) was shortened 6, 12, and 24 months after RYGB or SG.<sup>71,72</sup> In contrast, Ay et al observed a prolonged lag time 24 months after RYGB or GB.<sup>57</sup> Normally, a decrease in ETP and thrombin peak is accompanied by a prolongation of lag time, but a decrease in lag time might be a consequence of the surgery-induced lowering of TFPI and fibrinogen, both of

which contribute to the shortening of lag time.<sup>78</sup> This might also explain the previously reported shortening of PT time. Another source of variation is the use of different TF concentrations (1, 5, or 20 pM) in the TG test.

The results from the global plasma coagulation assays were in one study<sup>59</sup> confirmed by whole blood TEG. This method is used to obtain information about the viscoelastic properties of whole blood during coagulation, and TEG measurements showed a less hypercoagulable state 6 months after obesity surgery with longer reaction time and decreased maximum amplitude after an average BMI reduction of 22%.<sup>59</sup> Another study could not confirm this and observed unchanged values for all TEG variables after 6 months and a mean weight loss of



16%.<sup>74</sup> To our knowledge, no other studies have applied viscoelastic methods such as TEG or thromboelastometry on samples obtained beyond one month postsurgery.

### Obesity Surgery and Fibrinolysis

Overall, obesity surgery has a favorable effect on the impaired fibrinolysis associated with obesity. As outlined in ►Fig. 2, a reduction in fat mass is accompanied by a reduced synthesis of the central fibrinolytic inhibitor PAI-1 from adipocytes, the liver, platelets, and endothelial cells, and PAI-1 is the most investigated hemostatic biomarker after obesity surgery. In line with this, there is substantial evidence that GB and RYGB reduce concentrations of PAI-1 (PAI-1:Ag) 3, 4, 6, 12, 18, and 24 months after surgery,<sup>38,46,57,69,70,72,79–83</sup> with an average reduction of 48%. Further, two studies have observed a decrease in PAI-1 activity 6 and 12 months after vertical gastric stapling<sup>68</sup> or GB,<sup>45</sup> and Pardina et al demonstrated diminished PAI-1 mRNA expression from the liver 6 months after RYGB and from subcutaneous adipose tissue 6 and 12 months after RYGB.<sup>38</sup> Also, endothelial cells produce increased amounts of t-PA in obesity (►Fig. 2), and obesity surgery is accompanied by a decrease in t-PA:Ag.<sup>22</sup> Estimating the net effect on fibrinolysis, the “fibrinolytic capacity” in the euglobulin fraction of plasma<sup>84</sup> was higher 6, 12,<sup>68</sup> and 24<sup>72</sup> months after RYGB, and the t-PA induced fibrinolysis, assessed by whole blood TEG, increased 6 months after surgery.<sup>59</sup>

The effect on fibrin degradation can be estimated by D-dimer, which was lowered 12 and 24 months after RYGB or GB,<sup>66,72</sup> whereas a decrease 6 and 12 months after RYGB or SG did not reach statistical significance.<sup>71,72</sup> In these studies, D-dimer was measured with the STA-Liatest which has a lower detection limit of 0.27 mg/L. Since the postsurgery median D-dimer concentration was 0.27<sup>71</sup> and 0.35 mg/L,<sup>72</sup> respectively, D-dimer levels were close to the lower detection limit of the assay. Another study did also not observe a change in D-dimer 6 months after RYGB, but in this study the D-dimer assay was not described.<sup>74</sup>

### Obesity Surgery and Fibrin Clot Characteristics

A prothrombotic state can lead to increased fibrin clot formation, which makes the fibrin clot essential with respect to thrombotic risk. A prothrombotic clot phenotype is characterized by a more compact fibrin network with smaller pores and thinner fibers and with decreased clot permeability and lysisability.<sup>85</sup> Only two studies have focused on *in vitro* fibrin clot structure and lysis after bariatric surgery.<sup>72,86</sup> In both studies, the surgical method was RYGB, and fibrin clot lysis was significantly increased 6,<sup>72</sup> 12,<sup>86</sup> and 24 months after surgery.<sup>72</sup> Also, the fibrin fibers were formed more slowly (the maximal turbidity increment,  $V_{\max}$  was reduced), the fibers were thinner (decreased fiber mass–length ratio and fiber diameter) and had a higher density (increase in fiber density although only after 6 months).<sup>72</sup> Except for the increase in fiber density, this suggests an improved fibrin clot structure more prone to lysis after RYGB. Fibrinogen is an important determinant of the fibrin clot, and the reduction in fibrinogen<sup>38,45,64,68–72</sup> might partly explain effects on fibrin characteristics after obesity surgery. However, effects on the

fibrin fiber network and the clot lysisability are complex and depend on multiple factors,<sup>87</sup> and more studies are needed to identify determinants of surgery-induced changes in fibrin clot characteristics.

In summary, results from studies on coagulation, fibrinolysis, and fibrin clot characteristics demonstrate that obesity surgery shifts the hemostatic balance in the antithrombotic direction. For a few biomarkers, the evidence is substantial (fibrinogen and PAI-1) with average effect sizes of 17 and 48%, respectively, but for most biomarkers there is only moderate or weak evidence (►Table 2).

## Discussion

Obesity surgery affects a high number of hemostatic biomarkers (►Table 2) and effectively reduces body weight. Further, surgery favorably affects lipids, glucose, insulin, HbA1c, and insulin resistance.<sup>88</sup> It is unknown, whether the hemostatic changes are mediated by weight loss alone or by the accompanying metabolic improvements. In one study, Lupoli et al compared RYGB and SG with respect to 13 hemostatic biomarkers 2 months after surgery, and the surgical techniques affected weight loss equally, but eight of the measured biomarkers were significantly lower after RYGB than after SG.<sup>75</sup> Thus, RYGB, which in contrast to SG is associated with intestinal malabsorption, seems to be superior to SG with respect to effects on several hemostatic biomarkers 2 months after surgery, although long-term effects are unknown. The study also suggests that weight loss is not alone responsible for effects on hemostasis. This is supported by the lack of significant correlations between changes in body weight and changes in hemostatic biomarkers in all except four studies in ►Table 1.<sup>45,65,74,89</sup> Also, multivariate regression analysis indicated that changes in cholesterol and HOMA-IR, as a measure of insulin resistance, are the most important determinants of changes in thrombin peak 2 years after surgery.<sup>57</sup>

To disclose whether the effects of RYGB depend on comorbidity of the patient, Ferrer et al divided patients into three groups according to presence/no presence of type 2 diabetes and/or dyslipidemia showing that comorbidity significantly affected changes in PT, AT, and fibrinogen, but not changes in PAI-1 and APTT.<sup>70</sup> These results were supported by significant reductions in TF, FVII:Ag, F1 + 2, total and free TFPI only in patients with impaired glucose tolerance.<sup>64</sup> However, these subgroup analyses included a low number of patients.

A drawback of all the studies in ►Table 1 is that no parallel control group was included. An appropriate control group is difficult to obtain in studies of bariatric surgery and might not be considered ethically acceptable since the control group cannot be offered the best treatment option. Alternatively, a cohort of weight- and age-matched individuals not seeking bariatric surgery, but followed over time in parallel to the surgery group can be used as controls. More optimal, but even more complicated, the control group must follow the same lifestyle (diet and exercise) as the postsurgery cohort. Thereby, effects of surgery-induced weight loss and metabolic improvements can be separated from effects of the pronounced changes in diet brought about by the restricted intake after

surgery. Various dietary components have well-known effects on hemostasis without affecting body weight.<sup>90</sup> Also, exercise levels might increase after surgery. This is rarely reported, but we have shown that self-reported and accelerometer-reported physical activity was not affected 6 months after RYGB.<sup>91</sup> In practice, however, it is not possible or relevant to separate effects of diet and surgery on weight loss because pronounced dietary restrictions are unavoidable and the main reason for weight loss after surgery.

In contrast, it seems relevant to discuss if medication discontinuation after surgery is confounding the hemostatic results. Patients with obesity are very heterogeneous with respect to comorbidities and receive various medications, for example, statins and metformin, and many of these drugs affect hemostasis and are discontinued after surgery. Confounding by medication can be avoided by studying medication-free patients. Only two studies have included medication-free patients, and both studies observed significant improvements in several hemostatic biomarkers after GB<sup>45</sup> and RYGB,<sup>72</sup> thereby suggesting that the favorable effects on the hemostatic balance are not caused by medication discontinuation. Medication might also contribute to explain the lack of correlation between changes in body weight and changes in hemostatic biomarkers, and in medication-free patients correlations were observed between changes in body weight and changes in fibrinogen, PAI-1:Ag, vWF, and FVII.<sup>45</sup>

Finally, all studies are confounded by difficulties related to blood sampling in people with obesity. Venepuncture of a straight, clean, and visible vein is the recommended blood sampling technique for coagulation analyses. However, the vein can be hard to access in people with obesity, and because this is more pronounced before than after surgery, there is an increased risk of presurgical coagulation activation caused by complicated blood sampling.

The findings regarding hemostatic biomarkers (► **Table 2**) indicate a reduced thrombotic potential with a decreased CVD risk after obesity surgery, but are the findings clinically important, or are they only small yet measurable changes without any clinical significance? Biomarkers represent surrogate endpoints that are expected to predict clinical benefit.<sup>92</sup> A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”<sup>92</sup> An appropriate biomarker for CVD predicts CVD and can be used to monitor disease progression.<sup>93</sup> Importantly, however, studies on biomarkers are valuable tools in understanding the mechanisms linking obesity to CVD.

It might be speculated whether the antithrombotic effects of obesity surgery have any negative consequences, for example, increased risk of bleeding and deficient wound healing. Thus, obesity has been associated with a lower risk of bleeding complications in some studies,<sup>94,95</sup> but not in others<sup>96</sup> and it is presently unclear if the prothrombotic state in obesity is sufficient to protect against clinically relevant bleeding. In contrast, the relation between obesity and perioperative deficient wound healing is well established,<sup>97</sup> and a reduction in fibrin clot formation after obesity surgery might therefore

impair wound healing. Most likely, however, deficient wound healing in obesity is caused by various mechanisms besides hemostasis, for example, anatomic features of adipose tissue and vascular insufficiency,<sup>97</sup> and weight loss after obesity surgery may in itself improve wound healing.

Focus of the present review is on blood coagulation and fibrinolysis, but also platelets are important players in hemostasis starting with platelet adhesion, activation, and aggregation with formation of the primary hemostatic plug. Only a few studies have investigated effects of obesity surgery on platelets. Thus, platelet counts decreased 3 and 12 months after obesity surgery and more significant after SG than after RYGB,<sup>98</sup> and washed platelets displayed a reduction in thrombin-induced platelet aggregation 1 year after RYGB.<sup>99</sup> More studies are needed to understand the effects of bariatric surgery on platelet function.

## Conclusion and Future Studies

The 25 studies included in this review show that obesity surgery favorably affects several biomarkers of coagulation and fibrinolysis. The evidence is substantial for fibrinogen and PAI-1 with average reductions of 17 and 48%, respectively. For most other biomarkers, the evidence is moderate or weak with average effect sizes varying from 2% for fiber mass length ratio to 70% for prothrombin fragment 1 + 2 and with a large variation between studies. Many studies are small and of short duration. Inconsistent findings were observed for AT, vWF, TFPI, F1 + 2, PT, D-dimer, time to peak, and lag time in the TG test (► **Table 2**), and this might be explained by differences in surgical techniques, medications, comorbidity, diet, exercise, hemostasis assays, and type 2 errors in small studies.

Several hemostatic biomarkers were significantly more reduced 2 months after RYGB than after SG despite comparable weight loss.<sup>75</sup> This was most pronounced for the vitamin K dependent coagulation factors and inhibitors, and in multivariate analysis RYGB was associated with increased risk of deficiency in FVII, protein C, and protein S. The authors speculated that vitamin K malabsorption might increase the postsurgery thrombotic risk due to a diminished coagulation inhibitor capacity.<sup>75</sup> More knowledge is needed in this area, and assessment of the inhibitor capacity should be extended with measures of TFPI, AT, and FVIIa-AT, important coagulation inhibitors with only sparse or no evidence after bariatric surgery.

No studies have examined how obesity surgery affects determinants of fibrin clot formation such as fibrinogen variants, TAFI, FXIII, plasminogen, and PI (► **Table 2**). Also, the effect of bariatric surgery on the contact activation pathway of coagulation is unknown, but APTT was unaffected in two studies.<sup>70,71</sup> The contact activation pathway comprises proteins such as FXII, FXI, high-molecular weight kininogen, and prekallikrein, and there is a well-known interplay between contact activation and inflammation.<sup>100</sup>

All studies included in this review obtained blood samples in the fasting state. We and others have reported postprandial activation of FVII in the hours after a high-fat meal,<sup>101–103</sup> but after obesity surgery, the meal size is highly restricted and the

intestinal absorption is decreased. The consequences for postprandial coagulation activation are unknown.

In conclusion, despite issues of confounding and lack of appropriate control groups, this review suggests that obesity surgery, with the inevitably accompanying weight loss, metabolic improvements, and changes in medication, comorbidity, diet, and exercise, shifts the hemostatic balance in the antithrombotic direction, thereby reducing the thrombotic potential in people with obesity. Confirmatory studies are needed for most of the biomarkers, and many questions are not answered yet.

#### Conflict of Interest

None declared.

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