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REVIEW ARTICLE

OBESITY AND THE CLOTTING CASCADE: MECHANISTIC INSIGHTS INTO HAEMOSTATIC ALTERATIONS

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Abstract

Obesity is linked to the disruption of haemostasis. Numerous studies have indicated that obese individuals exhibit higher plasma concentrations of all pro-thrombotic factors, such as fibrinogen, von Willebrand factor, and factor VII in comparison to non-obese individuals. Additionally, elevated plasma levels of plasminogen activator inhibitor-1 have been studied in obese individuals compared to non-obese individuals. Moreover, obesity is marked by heightened plasma concentrations of anti-thrombotic agents, such as urokinase plasminogen activator, tissue-type plasminogen activator, and proteins C and S. The rise in these agents may be seen as protective measures to mitigate the impacts of the increased pro-thrombotic factors. The molecular connections between coagulation and fibrinolytic systems facilitate the targeted and efficient breakdown of fibrin accumulations, ensuring continuous blood flow and minimizing blood loss. The link between obesity, endothelial dysfunction, and haemostasis suggests that obesity features elevated levels of von Willebrand factor, fibrinogen, tissue factors, factor VII, VIII, and FX, which have been noted to promote a hypercoagulable condition. Although the coagulation and fibrinolytic systems collaborate to maintain the haemostatic equilibrium of the system, the fibrinolytic system functions to orchestrate the interactions among activators, zymogens, enzymes, cofactors, receptors, and inhibitors of fibrinolysis, facilitating the breakdown of fibrin deposits at the injury site without causing systemic negative effects. Thrombosis linked to obesity is one of the leading global health issues, and thus, continuous updates in this field are essential for improved comprehension of this treatable yet widespread condition.

Keywords: Coagulation, fibrinolytic disorders, haemostasis, obesity.

INTRODUCTION

Haemostatic factors that are linked to the progress and development of obesity predisposition to cardio-vascular disease (CVD) are many, including fibrinogen (FN), factor VII, von Willebrand factor (vWF), tissue plasminogen activator (tPA) antigen and plasminogen activator inhibitor-1 (PAI-1)[1]. It has been shown that the secretion of inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1β (IL-1β) by adipose tissue, together with adipose tissue-expressed tumour necrotic factor-α (TNF-α) in obesity, could explain the linked between the coagulopathy, endothelial dys-function and coronary heart disease. Other bioactive substances, including leptin and some hormonal defects, such as androgen and catecholamines are also associated with the deposition of body fat, that may induce the impairment of coagulative and fibrinolytic pathways in obesity[2]. Fibrinolysis is a well-regulated system which combines with the coagulation cascade through several molecular mechanisms[3,4]. Many disorders of the coagulation cascade would have a significant effect on the fibrinolytic system, as the two systems are complementary to each other. In coagulation cascade, fibrinogen is recognised to be the most fundamental haemostatic-associated risk factor for CVDs, because of its involvement in plasma viscosity, platelet aggregation and fibrin formation. Fibrinogen promotes the thrombogenic effects for several risk factors, where it acts as an acute phase reactant that is increased in inflammatory conditions. The association between fibrinogen and low density lipoprotein (LDL)-cholesterol indicates that lipid imposed CVDs risk is induced partly through

fibrinogen. Furthermore, the Framingham Study concluded that fibrinogen and C-reactive protein (CRP) investigations could be essential screening tools for the detection of individuals at risk for thrombotic complications to CVDs[1]. Fibrin is generated from the final enzymatic proteolysis through coordinated interactions between the activators (enzymes) and inhibitors, that initiates an efficient action during vascular endothelial injury. Fibrinolytic system is extremely controlled by a protease enzymes inhibitor known as PAI-1, which is synthesized by endothelium, adipose tissues, and the liver. PAI-1 serves as a strong irreversible inhibitor of plasminogen activators, including t-PA and urokinase plasminogen activator (uPA), which play a very critical role during the conversion of plasminogen to plasmin, thereby promoting fibrinolysis. Most commonly, fibrinolytic disorders result from an imbalance between the inhibitors such as PAI-1, α2-antiplasmin (α_2-AP) and activators of fibrinolysis, including tPA, uPA and thrombomodulin (TM). Inhibitions of fibrinolytic activities occur mostly either at plasminogen activators levels by PAI-1 or at plasmin by α_2-AP[2]. Several reports have shown that the secretion of PAI-1 is highly elevated during obesity[3]. Some inflammatory markers, including TNF-α, have been shown to upregulate PAI-1 expression, indicating the association between increased PAI-1 anti-fibrinolytic activity and chronic inflammation in obesity[5]. Furthermore, the elevated biochemical markers of vascular endothelial cells, and platelet adhesion and aggregation molecules that are seen in obese patients were reported to be associated with the increased levels of inflammatory markers, particularly, the TNF-α[6]. Activated fibrinolysis due to congenital or acquired deficiency of fibrinolytic inhibitors is characterized by the bleeding diathesis. Individuals with acquired α_2-AP deficiency are associated with numerous pathological conditions, including severe liver disease (LDX), disseminated intravascular coagulation (DIC), nephrotic syndrome or thrombolytic therapy that has been reported to promote an extreme mobilization of the inhibitors. While primary congenital abnormalities of fibrinolysis are uncommon and are associated with thrombosis and bleeding episode, acquired fibrinolytic disorders, on the other hand, are frequent, and are characterized by secondary and other primary disorders or coagulation therapeutic interventions[7]. Although there is improved knowledge on the pathogenesis, management and prevention of haemostatic disorders associated with atherothrombosis in obesity, it has been proposed that the CVDs will be among the major cause of death worldwide by the year 2020[8]. This review summarizes an update on the mechanisms of haemostatic disorders associated with obesity, with a focus on coagulation and fibrinolytic systems. The links between haemostatic disorders and obesity, and the progress and development of thrombosis predisposition to CVDs substantially were elaborated. The implications and possible therapeutic measures to be adapted were also precisely discussed.

This review aims to provide a comprehensive synthesis of current evidence linking obesity to alterations in the haemostatic system, with a focus on the mechanistic pathways underlying prothrombotic risk.

Search strategy and study limitations

To ensure a comprehensive and current synthesis of the literature, we employed a structured search strategy across three major biomedical databases: PubMed, Scopus, and Web of Science. The search was conducted for articles published between January 2015 and June 2025, focusing on studies that elucidate the relationship between obesity and haemostatic alterations. Search terms included combinations of "obesity", "thrombosis", "coagulation", "PAI-1", "platelets", "endothelial dysfunction", "fibrinolysis", "extracellular vesicles,", "NETs", "gut microbiota", and "prothrombotic state." Boolean operators ("AND," "OR") were used to refine the searches, and filters were applied to select English language, peer reviewed original articles, reviews, and clinical studies. Inclusion criteria focused on studies involving adult human subjects or relevant animal models, with a clear investigation into the mechanistic, clinical, or epidemiological aspects of obesity associated haemostatic changes. Priority was given to articles that provided molecular insight, evaluated therapeutic interventions, or contributed novel findings on coagulation related biomarkers in obesity. Studies focusing solely on other components of metabolic syndrome without direct coagulation relevance were excluded.

Despite the rigorous search process, several limitations must be acknowledged. First, this is a narrative review, not a systematic review or meta-analysis, and thus it may be subject to selection bias in study inclusion and interpretation. While we strived to ensure balanced representation, the narrative format inherently involves a degree of subjective synthesis. Second, the potential for publication bias cannot be excluded; negative or inconclusive studies may be underrepresented in the published literature, potentially skewing the collective understanding of certain mechanisms or interventions. Third, while many observational and mechanistic studies were included, there remains a notable paucity of randomized controlled trials (RCTs) or large interventional studies specifically addressing thrombotic risk modification in obese populations. This gap highlights the ongoing need for prospective clinical research to validate mechanistic findings and inform evidence based therapeutic strategies. Furthermore, although global perspectives were considered, geographic disparities in available data particularly from low- and middle income countries limit the generalizability of some conclusions. Finally, as the field continues to evolve, newer concepts such as the gut microbiota–coagulation axis or neutrophil extracellular traps (NETs) in obesity induced thrombosis are still emerging and require more robust validation.

Haemostasis: An overview

Haemostasis is one of the protective processes that regulates and maintains stable physiology in the system. The physiologic mechanisms of haemostasis are very complex and reflect a crucial balance between constant blood flow and a quick localized response to vascular endothelial injury. It associates with other body defensive mechanisms, including the immune

system and the inflammatory responses[9]. During the vascular injury, the increased blood pressure exerted in the blood circulation requires a powerful and regulated localized pro-coagulant responses to minimize blood loss, without compromising blood flow. Systemic anti-coagulant and fibrinolytic components in other ways are also developed to inhibit the extension of the pro-coagulant responses to escalating beyond control during vascular injury, which may result in significant thrombus formation. Haemostasis is thus defined as a complex, well regulated and integrated processes, comprising both activators and inhibitory pathways that involves several components, including blood vessels, platelets activities, coagulation factors and fibrinolytic agents together[10]. Knowledge on the universal sequence of events in haemostasis can give vital information for understanding the thrombogenic mechanisms. Within the blood coagulation cascade, the extrinsic pathway is mostly initiated by endothelial injury, whereas the intrinsic pathway is triggered solely through the exposure of FXII on the thrombogenic surface. Even though separated, these pathways are interconnected at several points[11]. For example, factor FIX is converted to FIXa but the conversion can also be triggered upon its interactions with FVIIa. Eventually, both pathways are linked together to initiate the common pathway, that terminates by the generation of fibrin clots, which are subsequently dissolved by plasmin during fibrinolysis[12]. During tissue injuries, the endothelium might be destroyed, and the vascular constriction would be initiated by the neurogenic reflexes with the local production of some factors, such as endothelium derived endothelin (EDE). Within the injured vascular endothelium, platelet adhesion and activation are promoted by the exposed extremely thrombogenic subendothelial extracellular matrix (ECM). Eventually, a haemostatic plug, composed of platelet aggregates and other leucocytes is formed[11]. Hence, the transmembrane receptor, also known as tissue factor (TF), and described as factor III (FIII), is exposed at the sites of endothelial injury. Through its interactions with proconvertin (FVII), TF initiates the coagulation cascade by the conversion of prothrombin to thrombin. During the secondary haemostasis, the thrombin generated triggers the generation of fibrinogen which is eventually converted to an insoluble fibrin plug that formed a network of fibrin mesh together with aggregated platelets that were mobilized to the site of injury. This leads to the generation of solid plugs through the polymerization of fibrin together with platelet aggregates[11], which then stop the blood flow, thus ensuring "haemostasis," as the final step of the coagulation cascade[13]. As the "thrombus", the circulating blood cells become trapped into fibrin structure and fibrin cross-linked is accomplished by FXIIIa, promoted through thrombin, leading to solid structural stability and the initial step of the fibrinolytic system[14]. During repair mechanisms, the generated thrombus is dissolved by plasmin activities, which is produced by its zymogen plasminogen on the fibrin clot, either by tPA or uPA[15]. Proteolysis of fibrin generates soluble fibrin degradation products (FDPs)[16].

Recently, the cell based model of the haemostatic process was developed, as the mechanisms through which structural components influence the haemostatic system[17]. This model indicated that coagulation process is initiated on the platelets and TF-exposing cells through three phases, including initiation; which takes place at the tissue factor bearing cells, amplification; through which platelet and other co-factors are activated to trigger the increased production of thrombin, and finally, propagation, which facilitates the profound generation of thrombin on the activated platelets surface[17]. This model provides enough description of haemostasis from diversified views, as against the protein based model[17]. To maintain the normal haemostasis, the coagulation cascade and fibrinolytic system should act to control the vascular endothelial repair through the formation and degradation of fibrin clots respectively[18].

Obesity promotes haemostatic changes

Adipose tissue synthesizes adipokines which contribute essentially to the regulation of the pathophysiologic processes, including adipocytes differentiation, inflammation, immunity, glucose and lipids metabolic processes. Under normal physiology, the endothelium acts as an antithrombotic surface through the regulation of coagulation cascade activities[19]. Vascular endo-thelial cells (ECs) are the main components responsible for proinflammatory, procoagulant, and antifibrinolytic activities, and the counter balance effectors of the anti-inflammatory, anticoagulant and profibrinolytic properties. All these components are essential in the maintenance of physiologic balance associated with the vascular haemostatic system[20]. Obesity is well associated with the modifications of the normal composition of the adipose tissue. Moreover, accumulation of fat during obesity results in dysfunctional adipose tissue, which might progress to adipocytes hypertrophy. Adipocytes hypertrophy has been identified to alter the well coordinated balance between haemostasis and adipose tissue derived cytokines, leading to proinflammatory and prothro-mbotic states[21]. These might be responsible for the increased secretion of proinflammatory cytokines, such as IL-6, TNF-α, IL-1β, prothrombotic markers, including TF, FN, FVII, FVIII, TM, vWF, and endothelial infiltration by macrophages, which event-ually promotes inflammatory process[22]. Once activated, ECs secret procoagulant or antifibrinolytic agents and subsequent decreased in the production of anti-coagulant and profibrinolytic components, which further promote endothelial dysfunction[23]. Moreover, the activated macrophages available in adipose tissue have been investigated to synthesis TF, which together with increased liver production of FVII and FVIII facilitate the possible coagulation disturbances. Obesity is associated with prothrombotic effects triggered by chronic inflammation and impaired fibrinolytic processes, which could promote dysfunctional endothelium, atherosclerotic plaques rupture, platelet hyperactivities and hypercoagulability state, and prolonged fibrinolysis[3].

All these abnormalities are identified to facilitate significantly to the progress of the prothrombotic state

observed in obesity and its associated metabolic disorders[24].

Obesity and coagulation cascade

The coagulation cascade begins when TF is exposed to blood and binds to FVIIa. Obesity is associated with elevated TF-mediated coagulation and increased expression of adipocyte and TF-mediated monocyte. These further facilitate the increased levels of TNF-α, Ang II, C-RP and insulin. The high levels of FVII and VIII observed correlate with the measures of obesity, with an increased risk of CVDs. Studies had indicated that Factor VII and VIII, are strongly connected with venous thromboembolism (VTE), while the increased levels of total glycerides (TG), LDL, total cholesterol (TC) and subsequent decreased in the levels of high-density lipoprotein (HDL) are reported to be the main lipid disturbances observed during obesity[25].

Furthermore, several studies have also reported that hyperfibrinogenaemia is highly associated with the high prevalence and persistent CVDs and VTE, which correlate with measures of obesity seen, especially in women. Fibrinogen facilitates both venous and arterial thrombosis due to high fibrin formation, plasma viscosity and increased platelet aggregation.This could further promote atherosclerotic formation associated with vascular smooth muscle cells (VSMCs) and EC proliferation[25].

Obesity impairs fibrinolytic activities

The consistent increase in the prevalence of obesity has been recognized as one of the most global socio-economic condition occurring in recent years and is correlated to the progress and development of thrombotic disorders. Many other mechanisms, including endothelial dysfunction, systemic inflammation, disturbances in glucose and lipid metabolisms, and insulin resistance also contribute significantly to the hypercoagulable state seen in obesity[25]. Abnormal fibrinolytic activity may promote atherosclerosis through vascular luminal surfaces exposure to constant and intermittent microthrombi and clot related mitgens, which may further progress the development of atherosclerosis in obese subjects. Obesity enhances the secretions of prothrombotic markers, including FN, FVII, vWF and plasma viscosity. Several studies had reported the elevated levels of PAI-1 in obese compared to lean subjects, and both basal and enhanced fibrinolytic activities were reduced[26]. Since PAI-1 complexes with most of the tPA antigen and results in its inactivation, the decreased level of tPA antigen observed in obesity is reported to be linked with the high concentration of PAI-1 reported during obesity[27,29]. PAI-1 is reported to be upregulated in adipose tissue during obesity, and significant circulating levels of PAI-1 was demonstrated in human subjects with central adiposity[2]. Furthermore, the expression of PAI-1 has been investigated to be upregulated by TNF-α, which indicates that the increased PAI-1 fibrinolytic activity is associated with the chronic inflammatory state[29]. The molecular mechanism that linked obesity, high levels of PAI-1, and thrombosis have been demonstrated both in human and mouse models. Several studies have demonstrated higher plasma concentrations of PAI-1 in obese mice compared to lean mice. Nagai *et al.*[30], investigated that mice with PAI-1 deficiency are associated with complete retraction of artery occlusion (ischemic stroke mice), indicating the critical mechanistic function of PAI-1 in facilitating the prothrombotic effects in obesity. Furthermore, during obesity, adipocyte syntheses low concentration of adiponectin, through which platelets aggregation and the subsequent increased PAI-1 production are promoted. This would further inhibit fibrinolytic activity[20]. Obesity is characterized by the elevated levels of fibrin degradation products (FDP), possibly due to increased plasma cytokines stimulation of hepatic FN production, which facilitates the progress to inflammation during fibrinolytic cleaved to FDP-D and FDP-E. Since FN is linked to weight gain, this indicates that there is a significant correlation between obesity and the progress of inflammation in fibrinolytic disorders. Other reports also have shown that the transcriptional levels of TF are highly up-regulated in adipocytes of obese individuals compared to normal subjects[31].

Obesity influences platelet alterations

Obesity is a heterogeneous condition characterized by chronic low-grade inflammation and oxidative stress, which cause injuries to the endothelium, contributing to its loss of antithrombotic activities. This authen-ticates the hypothesis that obesity is a pro-thrombotic condition characterized by increased platelet activities, which may have a profound effect on the fibrinolytic system[32,33]. Platelets are the major contributors to thrombotic processes. In obesity, the modifications of platelet activities contribute significantly to the progress of thrombus formation and arterial occlusions, indicating that platelets could play a significant role in the progress and development of atherothrombosis during obesity[33]. Several reports have demonstrated a significant association between obesity and impaired homeostasis, leading to CVDs. Clinical features, including hypertension and disturbances in micro-haemorrheology, which were thought to be linked with a prothrombotic state that could predispose platelets to hyperaggregability and hyperactivation. Furthermore, several clinical markers of platelet were identified to be increased during obesity. These include the circulating levels of platelet microparticles, the mean platelet volume, oxidative stress products, soluble platelet derived P-selectin and CD40L, which explained the molecular link between obesity, inflammation, and thrombosis[33]. Obese subjects experienced abnormal platelets, known as “angrier”, which promote platelet activation and aggregability. These have been recognized as an associated risk factor for the development of atherothrombosis predisposition to CVDs[34]. Additionally, many reports linking proteomic analysis and platelet aggregation have demonstrated the evidence of modifications in proteins associated with platelet signalling during obesity[35]. Body mass index (BMI) is correlated with increased expression glycoprotein V (GPV), including the elevated concen-tration of Src (pTyr418) and tyrosine-phosphorylated phospholipase C2, which are necessary for integrin signalling. These also explained mechanistically the

reason for platelet hyperactivation during obesity. During obesity, platelet hyperactivity has been identified as the molecular link between leptin and adiponectin[36]. The in vitro experimental studies of human platelets revealed that leptin alone does not promote platelet aggregation but it facilitates the pro-aggregating consequences of sub-threshold levels of ADP and thrombin[13]. Furthermore, the leptin induced platelet activation specific pathway involving the Janus kinase 2 (JAK2), phosphatidylinositol 3 kinase (PI3K) and phospholipases C2 and A2, has a significant effect on 30, 50-cyclic adenosine monophosphate (cAMP) hydrolysis, GPIIb/IIIa synthesis, and thromboxane A2 (TXA2) expression. Also, the increased plasma concentration of leptin is associated with a high risk of thrombotic episodes, progressing to CVDs[13]. On the other hand, adiponectin exerts anti-inflammatory effects by protection against thrombotic events, insulin resistance, hyperlipidaemia, and endothelial dys-function. Adiponectin is a secretory protein synthesized by the adipocytes and released as a trimer which cleaved to form multimeric complexes that are active signalling transducer[37]. In the experimental mouse model, adiponectin was demonstrated to show elevated fatty acid oxidation, possibly due to the actions of AMP kinase (AMPK). Additionally, experimental adiponectin deficient mice revealed high platelets response to pro-aggregating and thrombotic tendencies[38], and elevated concentrations of plasma adiponectin have been linked with decreased risk of CVDs and high nitric oxide (NO) bioavailability[39].

Obesity and thrombosis

Chronic inflammatory state in obesity is characterized by major consequences of prothrombotic and signalling pathways in the endothelial cells. Stimulations of endothelial cells, platelets, and many circulating cells by proinflammatory cytokines resulting in the upregulation of adhesion molecules and procoagulant factors and the subsequent downregulation of regulatory anticoagulant proteins. These facilitate thrombin production and increased platelet activities[40]. The synthesis of TFhas been described as the initial stage of the coagulation process and is facilitated by the endothelial cells and monocytes through the obesity related cytokines, including TNF-α and IL-6[41]. The binding of TF to coagulation FVIIa results in the activation of FIX and FX and the subsequent production of thrombin through the prothrombinase complex. Inflammatory cytokines also promote the synthesis of other adhesion molecules, including P-selectin, which influences vascular endothelial–leukocytes and platelet–leukocytes interactions, to further promote thrombosis. Chronic inflammation has been attributed with the downregulation of other local anticoagulants, including TFPI, and the protein C anticoagulation systems[40]. Obesity induced inflammation has been associated with the increased plasma levels of various coagulation factors, such as FN, vWF, and FVIII, which are known to be activated through the inflammatory cytokines available on hepatocytes and endothelial cells. Obesity is also a well known risk factor to ischemic stroke, deep vein thrombosis (DVT), arterial thrombosis (AT) and pulmonary embolism (PE) in humans at different ethnicities[3,42]. An increased BMI has been recognized as one of the major risk factors for atherothrombotic diseases, including CVDs, stroke, and venous thrombo-embolism (VTE). High BMI and waist-to-hip ratio were demonstrated to have elevated concentrations of prothrombotic factors and impaired fibrinolytic activities. Excessive glucose intake can directly alter local fibrinolysis through the augmentation of PAI-1 secretion[28]. Since PAI-1 can be expressed by the adipocytes, adipocyte alterations in obesity could be explained by the increased concentrations of PAI-1 and subsequent reduction in fibrinolytic activities[28]. Furthermore, very low density lipoproteins (VLDL) can also promote the secretion of PAI-1 from vascular endothelial cells. The molecular link between obesity and prothrombotic state is justified by the intervention studies from Folsom and colleagues, who indicated that a combination of diet and exercise programs is characterized by decreased body weight and improved haemostatic profile. Fortunately, patients with increased levels of PAI-1 due to BMI and waist-to-hip ratio can have reversed treatment by intensive lifestyle interventions[28].

Complication of obesity related thrombosis

The Fibrinogen modification of the local secretions of soluble mediators that influence the obesity phenotype raised some vital points addressed by researchers. Notably, the pharmacological depletion or genetic elimination of either MCP-1 or TNF-α leads to substantial protections from the high fat diet (HFD)-induced insulin resistance and non-alcoholic fatty liver disease (NAFLD)[43]. However, the lack of either TNF-α or MCP-1 does not warrant protection from increased body weight and elevated adiposity[43]. This suggested that fibrinogen could modify the activities of adipocytes or preadipocytes by; the combination of soluble mediators, ATM-mediated mechanisms, pro-inflammatory mediators involvement or the combination of these mechanisms[44,45]. Metabolic inflammation processes predispose individuals to several metabolic disorders, including CVDs, NAFLD, type 2 diabetes (T2D), osteoarthritis, and several forms of cancers that are associated with comorbidities and mortalities rates in many developed countries[46]. Association studies have recorded the increased levels of circulating vWF, FN, FVII and other biomarkers of the coagulation cascade, such as thrombin-anti-thrombin [TAT] complexes, thrombin, FI, FII as well as D-dimer during obesity[47]. Also, BMI is associated with increased resistance of activated protein C (APC), possibly due to increased levels of FVIII[48]. A randomized Mendelian study investigated that the risk to develop DVT is elevated by 3.4-fold from obese subjects compared to normal subjects[37,49]. Eventually, these observations justified the assumption that obesity is a well known high risk factor for the development of the thromboembolic disease. A genetic association study has also demonstrated that there is an association between thrombophilia mutations and superficial vein thrombosis. Many thrombotic risk factors, including proteins C and S deficiencies, APC resistance, prothrombin G20210A are also found in subjects with non-alcoholic steatohepatitis (NASH), and advanced

liver fibrosis[50]. Furthermore, a study was conducted on mice genetically induced deficiencies or functional mutations in FN,FXIII, TM, or protease-activated receptor-1 (PAR-1), and were investigated for alterations in body weight, modifications in inflammatory and metabolic profiles in the liver and adipose tissue[44]. The reports revealed that there was a mechanistic association between increased proco-agulant activities and fibrinogen driven inflammatory responses in both the liver and adipose tissue. Additionally, in proof-of-concept studies by the direct thrombin inhibitor reported that inhibition of thrombin activity modifies the progress and severity of obesity[44].

Haemostatic disorders in obesity

Defects in the coagulation cascade and fibrinolysis create a molecular basis that linked obesity and thrombosis. Several reports have identified that obese subjects are characterized by elevated plasma concen-trations of all pro-thrombotic factors, such as FN, vWF, and FVII compared to normal subjects. Also, high plasma concentrations of PAI-1 have been observed in obese patients compared to normal controls, which also correlates with visceral fat[51]. Furthermore, obesity is also attributed to elevated levels of anti-thrombotic factors, including t-PA and protein C, compared to non-obese subjects. These increased were suggested to be protective responses to counterbalance the increasing effects of pro-thrombotic factors. Several studies have reported that the production of IL-6 by adipose tissue, together with the adipose tissue-expressed TNF-α activities in obesity, could signify the linked between glucose and lipid metabolisms, endo-thelial dysfunction, coagulation abnormalities, and CVDs[2]. Also, some hormonal conditions related to androgen and catecholamines are characterized by the deposition of body fat, which might contribute significantly to the impairment of coagulative and fibrinolytic pathways during obesity[51]. Obesity is progressively associated with extensive alterations in adipose tissue involving adipogenesis, angiogenesis and extracellular matrix proteolysis. The fibrinolytic system contributes greatly to these processes. This was supported by the studies done on nutritionally obesity-induced transgenic mice, which demonstrated the role of the fibrinolytic system in adipogenesis and obesity[29]. Other Studies on venous or arterial thrombosis in obese mice models also reported the impaired of fibrinolytic activity, which was confirmed as a prothrombotic risk associated with obesity[1].

Fibrin plays dual significant functions in haemostasis, in such a way that it functions as the final step of the coagulation process and the initial protein for the fibrinolytic system. Under normal physiology, the processes of fibrin deposition and removal are efficiently controlled, to ensure normal body haemostasis[16]. Particularly, fibrinolysis is effectively mediated by the fibrin structure of the fibrin-containing thrombus on the surface of the cells that express profibrinolytic receptors, the extent of thrombin production, activations of thrombus-related cells, including thrombocytes, fibrinogen isoforms and poly-morphisms, and the complete biochemical environ-ment[52]. The coordinated activities of the fibrinolytic system are established through the actions of various proteins, including receptors, activators, and inhibitors. However, alteration in this delicate balance leads to catastrophic pathophysiological complications that might have implications toward thrombosis or bleeding tendencies. Thrombotic episodes mostly result in cardiovascular diseases, including heart attacks and ischemic strokes.

Table 1: Most common human fibrinolytic disorder and some polymorphisms associated with thrombosis.

Protein Deficiency	Haemostatic Phenotypes	References
Annexin A2	No available report	16
Plasminogen	Homozygous: Ligneous mucositis, Impaired wound healing, Pseudo-membranes of the gingiva, ear, eye, respiratory tract infections, including bronchitis. Heterozygous: No sign and symptom reported	16
tPA	No available report	16
uPA	No available report	54
α2-AP	Homozygous: Prolonged bleeding following surgery or trauma; intramedullary haemorrhage and diaphysis of long bones. Heterozygous: Usually clinical signs, associated with mild or minor bleeding	16
PAI-1	Homozygous: Impaired wound healing, intermittent abortion or miscarriage, mild to moderate bleeding, menorrhagia. Heterozygous: Usually asymptomatic associated with minor bleeding	16
PAI-2	No available report	16
TAFI	No available report	16
Common Polymorphisms associated with fibrinolytic disorders		
Polymorphisms		
tPA Promoter 7531 CT	High risk of arterial thrombosis seen in certain populations	16
PAI-1 4G Promoter	High risk of venous thrombosis and slightly increased risk of venous thrombosis	55
TAFI Ala147thr	High risk for coronary arterial thrombosis/disease	16,17
TAFI Thr325Ile	Elevated levels of TAFI in circulation but no evidence of increased in thrombosis generally.	37,38

Abnormalities of the coagulation cascade and fibrinolytic system are mainly associated with arterial thrombosis, many different sets of thromboembolisms, and other bleeding disorders[53]. Several forms of acquired and congenital abnormalities of the fibrinolytic system in human have been identified and documented (Table 1).

Both congenital and acquired fibrinolytic disorders have been described as either being hyper- or hypofibrinolytic disorder. Primary congenital deficiencies of fibrinolytic activating factors (plasminogen, t-PA, and u-PA), are insignificantly associated with intravascular thrombosis[52]. On the other hand, primary congenital deficiencies of fibrinolytic inhibitors (α_2-AP and PAI-1) are rare, but some inherited bleeding disorders are identified and well-documented. PAI-1 or α_2-AP congenital deficiency or congenital haemophilia are characterized by bleeding disorders, including epistaxis, menorrhagia, and prolonged bleeding following surgical procedure or trauma[52]. In particular, PAI-1 insufficiency is greatly associated with moderate to mild bleeding, including epistaxis, menorrhagia, and prolonged bleeding following a surgical procedure or traumatic injury[56]. The elevated serum concentration of PAI-1 has been reported to contribute to the development of adipose tissue and subsequent progress to obesity. This indicates the complicated interaction between PAI-1 and obesity[57]. Increased levels of PAI-1 alter the normal clearance of fibrin and eventually induce thrombosis. Elevated PAI-1 levels are strongly associated with obesity measures and PAI-1 levels are significantly reduced by weight loss as demonstrated on obese individuals. Various factors, including free fatty acids, CRP, triglycerides, insulin, TGF-b, Ang II and TNF-a have been shown to increase PAI-1 expression and secretion in adipose tissue. Thus, the elevated PAI-1 levels observed during obesity could predispose those individual to micro- and macro-vascular endothelial dysfunction and subsequent venous and arterial thrombosis[58]. Congenital α_2AP deficiency is an uncommon autosomal recessive condition that initiates mostly during infancy or early age, characterized by delayed bleeding episodes[57]. In congenital hyperfibrinolytic disorders, bleeding resulting from α_2AP deficiency, medullary bone haemorrhage and prolonged umbilical bleeding in the new-born is predominantly observed. Hereditary a2-AP deficiency, also known as Miyasato disease has been identified and is associated with bleeding episode due to excessive fibrinolysis[58]. Congenital deficiency of uPA, tPA, or TAFI is not yet confirmed, reflecting that null mutations in these factors may lead to inter-uterine death. Deficiency of uPA was reported to facilitate cancer development and progression[59], whereas TAFI deficiency was linked to increased accumulation of fibrin, which has a significant effect on the liver cells[60]. Hypoplasminogenaemia is a quantitative condition associated with reduced plasminogen activity and is attributed with hydrocephalus and congenital conjunctivitis. Dysfibrinogenaemia is among the fibrinolytic disorders in obesity in which patients present with a tendency to thrombosis predisposition to bleeding, thrombosis, and thrombophilia. It is characterised by abnormal clot lysis and defective assembly of the fibrinolytic system due to plasmin resistance. Congenital dysfibrinogenaemia is uncommon while acquired dysfibrinogenaemia may be present in some conditions, including liver cirrhosis, multiple myeloma, trauma patients, amniotic fluid embolism, DIC and severe haemorrhage[57].

A Mechanistic continuum: Linking obesity severity to thrombotic risk

Emerging evidence suggests that the relationship between obesity and thrombotic risk exists not as a binary state but along a mechanistic continuum. This continuum reflects a progressive disruption of haemostatic homeostasis that parallels increasing obesity severity, whether defined by body mass index (BMI), waist circumference, or more precisely, visceral adiposity. As individuals transition from overweight to class III obesity, the magnitude and complexity of coagulation disturbances intensify, creating a gradated yet compounding prothrombotic phenotype[60]. At the mild end of the spectrum, overweight individuals may display subtle elevations in circulating inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These early changes prompt modest increases in hepatic synthesis of fibrinogen and C-reactive protein (CRP), and may initiate early endothelial activation. However, overt prothrombotic shifts in clotting factor levels are often not yet detectable[61]. As obesity progresses into more severe classes, particularly with increased visceral fat deposition, the haemostatic environment becomes increasingly dysregulated. One of the key mediators in this stage is plasminogen activator inhibitor-1 (PAI-1), an adipokine largely secreted by visceral adipose tissue. PAI-1 levels rise sharply in correlation with central obesity, contributing directly to impaired fibrinolysis and prolonged clot stability.

Simultaneously, endothelial cells begin to lose their anticoagulant phenotype, marked by reduced nitric oxide (NO) bioavailability and increased expression of adhesion molecules such as VCAM-1 and E-selectin. These changes not only promote leukocyte-endothelium interaction but also create a vascular microenvironment that favors thrombosis[62].

In individuals with severe obesity, a state of full-blown haemostatic dysregulation emerges. Platelet hyper-reactivity becomes a hallmark, with increased expression of activation markers such as P-selectin and glycoprotein IIb/IIIa. Platelets become more sensitive to subthreshold agonists, such as thrombin and ADP, leading to enhanced aggregation and microthrombus formation. Concomitantly, levels of procoagulant factors especially factor VII, factor VIII, and von Willebrand factor (vWF)—are significantly elevated, further tipping the haemostatic balance toward hypercoagulability[63]. Moreover, the chronic low-grade inflammation associated with obesity creates a feedforward loop. Adipose tissue-derived cytokines and adipokines fuel systemic oxidative stress and endothelial injury, which in turn amplify coagulation factor expression and platelet activation. This mechanistic interplay is not uniform; rather, it evolves

in a dose-dependent manner along with adiposity, highlighting a biologically plausible gradient of thrombotic risk[64]. Thus, obesity does not merely trigger a binary switch into a hypercoagulable state. Instead, it drives a stepwise amplification of prothrombotic mechanisms, beginning with low grade inflammation and progressing toward advanced endothelial dysfunction, platelet hyperactivity, and fibrinolytic impairment. Recognizing this continuum has both diagnostic and therapeutic implications. It supports the need for stratified risk assessment in obese individuals, not solely based on BMI, but also incorporating markers of coagulation, platelet function, and endothelial health. It also underscores the potential value of early interventions aimed at halting or reversing this haemostatic cascade before it culminates in clinical thrombosis[65].

Extracellular vesicles and Neutrophil Extracellular Traps (NETs): Emerging prothrombotic drivers in obesity

Beyond classical coagulation pathways, emerging evidence implicates extracellular vesicles (EVs) and neutrophil extracellular traps (NETs) as potent contributors to the prothrombotic state observed in obesity. These non-traditional mediators offer novel insight into the crosstalk between inflammation, immunity, and haemostasis in the obese host. Extracellular vesicles comprising exosomes, micro-vesicles, and apoptotic bodies are membrane bound particles released by activated or stressed cells. In obesity, the expansion of adipose tissue is associated with chronic low grade inflammation and increased EV release from various sources, including endothelial cells, adipocytes, monocytes, and platelets. These vesicles carry a cargo of bioactive molecules, such as tissue factor (TF), phosphatidylserine, and microRNAs, which have been shown to enhance thrombin generation and promote coagulation cascades. In particular, TF-bearing EVs are markedly elevated in obese individuals and are strongly associated with increased risk of venous thromboembolism and cardiovascular events. Their small size and high procoagulant surface area allow them to interact easily with platelets and coagulation factors, creating localized environments of intensified thrombin formation[66].

Neutrophil extracellular traps (NETs) represent another critical link between inflammation and thrombosis in obesity. NETs are web like chromatin structures expelled by activated neutrophils, designed to trap pathogens during infection. However, in the context of obesity, chronic metabolic stress and systemic inflammation serve as potent stimuli for NETosis. NETs can directly trigger platelet aggregation, activate factor XII, and expose procoagulant molecules such as histones and high mobility group box 1 (HMGB1), thereby initiating and propagating thrombus formation. Recent studies have shown elevated NET biomarkers such as citrullinated histone H3 and cell free DNA in the plasma of obese individuals, suggesting an ongoing subclinical activation of this thrombogenic pathway. Furthermore, NETs contribute to endothelial dysfunction and microvascular injury, compounding the thrombotic burden in obesity[67,68].

Therapeutic considerations: Targeting haemostatic alterations in obesity

The multifaceted prothrombotic profile in obesity necessitates equally multifactorial therapeutic strategies. As the mechanistic underpinnings of obesity related coagulation abnormalities become increasingly clear, targeted interventions are emerging that specifically address distinct components of the haemostatic imbalance—ranging from impaired fibrinolysis to platelet hyperactivity and endothelial dysfunction[61].

Inhibition of PAI-1 to restore fibrinolytic balance

Plasminogen activator inhibitor-1 (PAI-1) is consistently elevated in obesity and serves as a key mediator of impaired fibrinolysis. By suppressing tissue plasminogen activator (tPA), PAI-1 leads to reduced clot breakdown and enhances thrombus persistence. Therapeutic inhibition of PAI-1 has garnered increasing interest, with small molecule inhibitors (e.g., TM5441 and TM5614) showing promising antithrombotic and metabolic effects in preclinical models without inducing bleeding complications. Additionally, lifestyle interventions such as weight loss and insulin sensitization (e.g., metformin) have been shown to reduce circulating PAI-1 levels and may complement direct PAI-1 inhibitors[52-63].

Modulation of platelet reactivity

Platelets in obesity are hyperreactive, characterized by increased expression of surface P-selectin, elevated thromboxane A2 synthesis, and enhanced aggregation. These changes elevate the risk for arterial thrombosis and cardiovascular events. Antiplatelet agents, such as aspirin, remain a cornerstone of therapy; however, resistance to aspirin and clopidogrel is more common in obese individuals, necessitating personalized dosing strategies or alternative agents such as prasugrel or ticagrelor. Novel antiplatelet therapies targeting platelet activation pathways such as protease activated receptor-1 (PAR-1) antagonists are under investigation and may provide improved efficacy in this population[64,65].

Endothelial protection and anti-inflammatory strategies

Obesity induces endothelial dysfunction through chronic inflammation, oxidative stress, and insulin resistance, all of which contribute to a procoagulant endothelial phenotype. Pharmacological agents that restore endothelial integrity such as statins, ACE inhibitors, and GLP-1 receptor agonists not only improve metabolic parameters but also exhibit antithrombotic properties by enhancing nitric oxide bioavailability and reducing endothelial expression of adhesion molecules and tissue factor. Furthermore, emerging therapies targeting inflammation such as IL-1β blockade (e.g., canakinumab) have shown promise in reducing vascular events and may mitigate endothelial-driven coagulation activation in obese patients[66,67].

Gut microbiota modulation

Given the increasing evidence of a gut microbiota coagulation axis in obesity, interventions aimed at restoring microbial homeostasis may also yield haemostatic benefits. Probiotics and prebiotics have been shown to modulate gut barrier function, reduce systemic endotoxemia, and downregulate inflammatory cytokines that promote coagulation. Additionally, trials of fecal microbiota transplantation (FMT) in obesity have demonstrated improvements in insulin sensitivity and inflammatory markers, suggesting a potential adjunctive role in modifying thrombotic risk[68].

Novel anticoagulant strategies

While traditional anticoagulants such as warfarin and low molecular weight heparin are effective, they pose challenges in the context of obesity due to altered pharmacokinetics and difficulty in achieving therapeutic dosing. Direct oral anticoagulants offer more predictable profiles and are increasingly used, although evidence specific to obese populations remains limited. Emerging agents, such as factor XI inhibitors (e.g., abelacimab), are currently under investigation and may provide safer long term anticoagulation with reduced bleeding risk[69].

Diagnostic and therapeutic challenges in LMICs: A Sub-Saharan African perspective

The relationship between obesity and thrombosis creates a major clinical challenge worldwide; however, in low- and middle-income countries (LMICs) especially in Sub-Saharan Africa the diagnostic and treatment environment is particularly intricate. These areas encounter a combination of systemic issues that intensify the challenges of identifying and addressing obesity linked haemostatic irregularities[66]. A significant barrier exists due to restricted access to sophisticated diagnostic equipment. Standard laboratory tests for assessing thrombophilic disorders like D-dimer levels, fibrinogen activity, platelet function assessments, or tests for protein C, protein S, antithrombin III, and lupus anticoagulant are frequently lacking or too costly in various LMIC environments. Moreover, the technical infrastructure necessary for newer biomarkers, such as plasminogen activator inhibitor-1 (PAI-1), endothelial cell markers, or NET-derived proteins, is generally confined to a limited number of urban referralcenters, resulting in many people remaining undiagnosed and undertreated[67]. Compounding this issue are concurrent infections that are prevalent in the area, including malaria, HIV, tuberculosis, and helminthic diseases each of which independently impacts coagulation pathways. For example, HIV infection is recognized to trigger a procoagulant condition through ongoing immune activation and endothelial impairment, whereas malaria leads to thrombocytopenia and disseminated intravascular coagulation (DIC). These infectious comorbidities can conceal, imitate, or worsen obesity related clotting disorders, complicating precise diagnosis further[68].

Malnutrition and micronutrient shortages continuing to exist in some areas of Sub-Saharan Africa represent another overlooked issue. Lack of essential nutrients like vitamin K, folate, and iron can change clotting patterns, either by affecting the production of coagulation factors or altering platelet activity. The phenomenon of "double burden malnutrition", in which undernutrition and obesity coexist in the same population or even an individual, produces a highly unpredictable haemostatic environment that adds complexity to clinical decision making[69]. From a treatment perspective, anticoagulation therapy is frequently limited by expense, variable accessibility, and the absence of monitoring systems. Although direct oral anticoagulants have certain benefits compared to warfarin, their expensive price and restricted availability impede broad adoption. In numerous instances, healthcare providers must depend on low-dose aspirin or inadequate warfarin treatments without INR monitoring methods that may provide minimal defense against thrombosis or increase the risk of bleeding for patients[70].

Moreover, cultural and systemic obstacles like health illiteracy, stigma associated with obesity, and inadequate integration of preventive care further impede early diagnosis and ongoing management. In certain communities, obesity might still be perceived as an indicator of affluence or wellness, postponing medical care until issues develop. Additionally, health systems in these areas frequently face overwhelming demands from infectious disease control and may be inadequately equipped for comprehensive management of non-communicable diseases (NCDs)[71]. To tackle these inequalities, there is an immediate requirement for regional guidelines, affordable diagnostic procedures, and funding for point-of-care testing. Approaches that shift tasks to non-specialist healthcare providers, promote community health education, and incorporate obesity related thrombosis into national NCD strategies are crucial advancements. Research conducted in collaboration with African populations that considers regional aspects like infection rates, dietary habits, and genetic factors is essential for guaranteeing that upcoming interventions are both grounded in evidence and relevant to the context.

Future Directions

Even though there is increasing awareness of the complex link between obesity and haemostatic dysfunction, significant gaps still exist in our knowledge especially in converting mechanistic findings into practical clinical approaches. Subsequent studies should focus on a more refined strategy for risk stratification and intervention, customized to the intricate diversity of obese groups[72]. A crucial approach involves creating personalized thrombotic risk assessments that extend beyond body mass index (BMI) to include visceral fat, inflammatory markers, platelet function tests, genetic factors, and new measures like extracellular vesicle profiles and NET markers. These multi-parametric models could facilitate the early detection of high risk individuals, inform the level of preventive treatment, and track responses to lifestyle or medication interventions with improved accuracy[73]. Furthermore, there is an urgent requirement for extensive, forward looking clinical studies that focus on assessing antithrombotic approaches in overweight persons. Most existing

guidelines are derived from general populations, which might not sufficiently represent the changed pharmacokinetics and hemostatic characteristics observed in obesity. Studies evaluating the effectiveness, safety, and appropriate dosing of anticoagulants and antiplatelet medications in this group are urgently needed[73].

Research cohorts also need enhanced diversity. Most current data originate from Western populations, resulting in considerable knowledge gaps regarding how ethnicity, geography, and socio-economic status influence thrombotic risk in obesity. For instance, populations in Sub-Saharan Africa and South Asia might display distinct inflammatory or coagulation characteristics owing to genetic, dietary, or environmental influences. Subsequent research should guarantee representation from various ethnic groups and areas to improve the applicability of results and assist in developing region specific recommend-dations[69]. Another overlooked aspect is the relationship between obesity and novel coagulopathy factors, including gut microbiota, epigenetic changes, and disruptions in circadian rhythms. Comprehending how these elements interact with the coagulation cascade in obese people may reveal novel therapeutic targets and improve existing treatment strategies[70]. Ultimately, collaboration across disciplines will be crucial. Connecting haematology, endocrinology, cardiology, immunology, and systems biology will enable the incorporation of omics technologies, machine learning, and digital health tools into the prediction and management of thrombotic risk[71]. With rising obesity rates worldwide, enhancing our understanding of thrombosis linked to obesity is both a scientific requirement and a public health essential. Concentrated, inclusive, and translational research initiatives will be crucial for alleviating the burden of thrombotic issues in the obese population.

CONCLUSIONS

Obesity creates a complicated and multifactorial prothrombotic condition marked by the disruption of coagulation pathways, decreased fibrinolysis, increased platelet reactivity, and endothelial impairment. Increased levels of PAI-1 have been consistently identified as a key factor in diminished fibrinolytic ability in obese individuals, significantly enhancing thrombotic risk. Furthermore, new findings indicate that extracellular vesicles and neutrophil extracellular traps (NETs) play significant roles as new pro-thrombotic elements in obesity, increasing coagulation activation and vascular inflammation. The microbiota coagulation connection in the gut is an advancing area of study that associates obesity related dysbiosis with systemic inflammation and coagulation disturbances, highlighting the promise of therapies aimed at the microbiome.

Additionally, regional inequalities particularly in low- and middle-income nations exacerbate diagnostic and treatment difficulties because of scarce resources, simultaneous infections, and malnutrition, making thrombotic risk management even more complex in these groups. Therapeutic approaches targeting critical pathological processes such as PAI-1 inhibition, alteration of platelet activity, protection of endothelial function, and normalization of gut microbiota provide encouraging options to alleviate thrombosis related to obesity, though clinical trial findings are still sparse. Ultimately, deficiencies in the existing evidence base, including a lack of extensive interventional studies and the underrepresentation of various populations, emphasize the pressing requirement for future research to create personalized thrombotic risk models and improve treatment approaches.

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AUTHOR'S CONTRIBUTION

Obeagu EI: conceived the idea, writing the manuscript, literature survey. **Kwaifa IK:** editing, critical review. Final manuscript was checked and approved by both authors.

DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

None to declare.

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