Thrombosis in central obesity and metabolic syndrome: Mechanisms and epidemiology

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Summary

Central obesity is a key feature of the metabolic syndrome (metS), a multiplex risk factor for subsequent development of type 2 diabetes and cardiovascular disease. Many metabolic alterations closely related to this condition exert effects on platelets and vascular cells. A procoagulant and hypofibrinolytic state has been identified, mainly underlain by inflammation, oxidative stress, dyslipidaemia, and ectopic fat that accompany central obesity. In support of these data, central obesity independently predisposes not only to atherothrombosis but also to venous thrombosis.

Keywords

Haemostasis, metabolic syndrome, visceral obesity, thrombosis

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Received: January 29, 2013
Accepted after major revision: April 20, 2013
Prepublished online: June 13, 2013
doi:10.1160/TH13-01-0075
Thromb Haemost 2013; 110: 669–680

Introduction

Central obesity corresponds to excess intra-abdominal adipose tissue (AT) and is part of a phenotype including decrease in subcutaneous adipose tissue expansion and ectopic triglyceride storage in different organs (mainly liver, pancreas, muscle). The association of the metabolic alterations closely linked to this condition is known as the metabolic syndrome (metS). MetS is a clinical entity of substantial heterogenous traits represented by the co-occurrence of central obesity, impaired glucose tolerance, dyslipidaemia (high triglycerides and low high-density lipoprotein [HDL] cholesterol levels) and hypertension. The conference on metS definition of the American Heart Association underlined two additional components that are a proinflammatory and a prothrombotic states and confirmed cardiovascular disease as major clinical outcome (1). MetS represents a public health concern because its prevalence is steadily increasing worldwide (2). Although the prevalence of the components of the metS is increased in obesity (3), it is important to notice that not all obese subjects (body mass index [BMI] >30) develop metS, and that non-obese individuals accumulating visceral fat can carry cardiometabolic risk factors and metS.

Visceral AT accumulation varies according to age, gender, genetics and ethnicity. Specific mechanisms responsible for proportionally increased visceral fat storage when facing positive energy balance and weight gain may involve sex hormones, local cortisol production in abdominal ATs, endocannabinoids, growth hormone, and dietary fructose (4). Pathophysiology of the central obesity mainly involved three interconnected pathways: (i) accumulation of ectopic fat (visceral AT, liver fat, pancreatic fat etc.) that exerts mechanical stress and delivers damaging molecules locally (ii) insulin resistance (IR), in which the cells fail to respond to the normal actions of the hormone and (iii) a constellation of circulating factors (e.g. molecules of hepatic, and adipose origin) that mediate specific components of the syndrome and contribute to cardiovascular disease.

In this review we describe the relationships between central obesity, the components of metS and alterations in hemostasis that may predispose to thrombosis. We provide epidemiological data on the contribution of central obesity to venous thrombosis.

Platelet dysfunction

Platelet hyperactivity is seen in individuals with the metS (►Table 1). This is supported in part by elevated cytosolic Ca^{2+} (5, 6), increase isoprostane and thromboxane A2 (TxA2) production from arachidonic acid (7), resistance to the antiaggregating effects of nitric oxide (NO) donors, prostaglandin (PG)I2 and their effectors, cGMP and cAMP (8). Surface expression of P-selectin and glycoprotein (GP)IIbIIIa mediating platelet-leukocytes conjugates and fibrinogen binding respectively are both increased in patients with the metS (9, 10).

These platelet modifications may be induced by the metabolic changes that accompany the metS, mainly IR, dyslipidaemia, oxidative stress, adipokines and inflammation (8, 11).

Loss of platelet inhibition by insulin has been suggested to be a major determinant of platelet hyperactivity during obesity (8). This may explain the association between diabetes and resistance to the antiplatelet effects of clopidogrel (12, 13) as insulin mediates

suppression of adenosine diphosphate (ADP)-induced P2Y12 signalling (14). Insulin resistance also explains the impaired ability of prostacyclin to increase cAMP synthesis, of cAMP to reduce platelet function and of NO to increase cAMP in platelets from obese subjects (15-18).

Weight loss simultaneously reduces IR and platelet hyperactivity (19, 20). Insulin also inhibits splicing of tissue factor (TF) pre-mRNA in platelets adhering to prothrombotic proteins and the loss of insulin responsiveness might well contribute to the thrombogenicity of the platelet plug that forms upon plaque rupture (21).

Hypertriglyceridaemia and increased concentration of free fatty acids exert a proaggregating effect *in vitro* (22). Hypo-HDLaemia influences platelet aggregation, possibly because HDL opposes the activation properties of low-density lipoprotein (LDL) on platelets (23). The exact mechanisms of these effects are not clearly elucidated. Oxidative stress has been identified as one of the factors closely associated with platelet hyperactivation in diabetes and

Table 1: Main mechanisms supporting platelet hyperactivity during visceral obesity.

Observed platelets defects	Proposed triggers	Main related references*
Increased adhesiveness, aggregation and procoagulant activity		Anfossi, Nutr Metab Cardiovasc Dis. 2009 (8) (review)
	Dyslipidaemia	Englyst, Diabetes. 2003 (22) Korporaal, Pathophysiol Haemost Thromb. 2006 (23)
	LDL oxidation	Colas, Diabetologia. 2011 (26)
	Adipokines	Konstantinides, J Clin invest. 2001 (29) Nakata, Diabetes. 1999 (30)
	Insulin resistance	Basili, J Am Coll Cardiol. 2006 (20) Ferreira, Arterioscl Thromb Vasc Biol. 2006 (14) Westerbacka, Arterioscl Thromb Vasc Biol. 2002 (19)
	Increased isoprostane (8isoPGF2a) and TXA2 production	Davi, JAMA. 2002 (7) Patrono, Curr Opin Pharmacol. 2005 (25) (review)
	Resistance to the antiaggregating effect of NO Donors, PGI2, cGMP and cAMP	Anfossi, Diabetes Care. 1998 (15) Anfossi, Eur J Clin Invest. 2004(16) Russo, Clin Chem. 2007(18) Russo, Obesity 2010(17)
Increased expression of platelet surface receptors	Oxidation	Anfossi, Cardiovasc Hematol Agents Med Chem 2006 (10) Arteaga, Am J Cardiol. 2006 (9) Cabeza, Diabetes. 2004 (36) Neubauer, Diabet Metab. 2010 (44)
Increased intraplatelet Ca^{2+}	Insulin resistance	Takaya, J Lab Clin Med 1997 (5)Touyz, J hypertens 1994 (6)
Increased mean platelet volume	Inflammation Non alcoholic steatohepatitis	Arslan J pediatr Endocrinol Metab. 2010 (52) Coban, Int J Clin Pract. 2005 (50) Muscari, Thromb Haemost. 2008 (49) Ozhan, Platelets. 2010 (51) Tavil, Thromb Res. 2007 (53)
Elevated levels of circulating platelet microparticules	Oxidation	Helal, Nut Metab Cardiovasc Dis. 2010 (27)
Increased Tissue Factor platelet expression	Insulin resistance	Gerrits Diabetes.2010 (21)
Increased platelet inflammatory status	Oxidation Advanced glycated endproducts Inflammation Adipokines	Angelico, Diabetologia. 2006 (38) Cipollone, Diabetologia. 2005 (41) Desideri, JAMA. 2003 (34) Genc, Clin Biochem. 2012 (40) Neubauer, Diabet Med. 2010 (44) Restituto, J Physiol Endocrinol Metab. 2010 (43) Santilli, Intern Emerg Med. 2007 (35) Varo, Diab Vasc Dis Res. 2005(39) Vaidyula, Diabetes. 2006 (42)

*Number in brackets corresponds to the reference list.

lipid hydroperoxides and advanced products of oxidation such as isoprostanes have been shown to stimulate platelet aggregation (24, 25). This was also recently described in patients suffering metS (26). LDLs from metS patients exhibit an increased oxidative stress. They activate platelets and prime collagen-induced platelet aggregation. The activation occurs through an increased phosphorylation of p38 MAPK, and resulted in an increased formation of TxA2 (26). In addition oxidative stress has been associated with high levels of microparticles originating from platelets, key protagonists in cardiovascular disorders, in subjects with metS (27).

Adipokines directly alter platelet function. Leptin potentiates the normal response of platelets to ADP and thrombin (28-30). In vitro platelet aggregation induced by low concentration of agonists was enhanced in adiponectin knockout mice and recombinant adiponectin overcame the enhanced platelet aggregation (31, 32). This aspect is treated in a much greater detail in this current Theme Issue.

Increasing evidences have suggested that platelets exert other roles beyond their well-recognised function in haemostasis and thrombosis. Platelets conduct immunoregulation through secretion of functional mediators, interaction with various immune cells, endothelial cells and influence angiogenesis (33). Circulating soluble (s)CD40L arises largely from platelets and plays a pathogenic role in atherosclerosis in regulating immune responses and inflammation. Increased circulating sCD40L levels were reported in obese (34, 35), type 2 diabetic patients (36, 37) and in carriers of metS (38). This may be consistent with an enhanced platelet activation that releases its inflammatory content in the circulation. Interestingly patients with type 2 diabetes show elevated levels of intracellular and membrane-bound platelet CD40L as well as sCD40L (39, 40). In addition, platelet surface CD40L expression and sCD40L levels are significantly correlated with key diabetes markers (HbA1c and advanced glycated end products) (41), are increased during hyperglycaemia and hyperinsulinaemia in clamp studies (42) and diminished by adiponectin (43).

These results suggest the contribution of glucose homeostasis to the bioavaibility of this key platelet inflammatory receptor (44). Improved glycaemic control helps to correct abnormal platelet activation via down-regulation of CD40-CD40L system (45). In addition, we previously showed that CD40L may affect adipocyte biology underlying an unsuspected relation between platelet products and obesity (46). Despite being anucleated cells, platelets have the ability to process mRNA into proteins. Several inflammatory platelet-derived mRNA have been associated with higher BMI supporting the hypothesis that excess adiposity may critically modulate the inflammatory capacity of platelets (47).

Apart from changing platelet functions through direct interference, metS may alter the properties of platelets during their synthesis from megakaryocytes (MK). Recent findings illustrate that resistin and leptin induce IR in megakaryocyte by interfering with insulin receptor substrate 1 through stimulation of the JAK/STAT pathway (48). A consistent, significant shift of the volume distribution to larger platelets was found in diabetics, obese people (49, 50), in patients suffering non-alcoholic fatty liver disease (51, 52) and in subjects suffering from metS (53). The reason for these changes is unclear, but it is likely that changes in MK are in part responsible. Indeed shift in ploidy has been described in type 2 diabetes due in part to an increase in the circulating level of interleukin (IL)-6 (54) that is overproduced during central obesity.

Hypercoagulability

Hypercoagulability is also part of the metS (▶Table 2). Plasma from subjects with the metS formed denser clots compared with subjects free from metS. In addition clot density increased pro-

Table 2: Main mechanisms supporting hypercoagulability during visceral obesity.

Observed coagulation defects	Proposed triggers	Main related references*
Elevated levels of circulating and monocyte tissue factor	Insulin resistance Adipokines	Diamant, Circulation 2002 (58) Kopp, Obes Res 2003 (63) Napoleone, J Thromb Haemost 2007 (60) Samad, Proc Natl Acad Sci 1998 (61) Samad, Blood 2001 (62) Vaidyula, Diabetes 2006 (42)
Increased clot density	Inflammation	Carter, Arterioscl Thromb Vasc Biol 2008 (55)
Elevated levels of vitamin K-dependent coagulation proteins	Non-alcoholic steatohepatitis Dyslipidaemia Inflammation	Bell, Hepatology 2010 (52) Carvalho, Haemostasis 1989 (73) Grant, J Intern Med 2007 (74) Godsland, J Clin Endocrinol Metab 2005 (65) Sakkinen, Am J Epidemiol 2000 (64)
Elevated levels of fibrinogen and factors VIII, IX, XI, XII	Inflammation Non-alcoholic steatohepatitis Endothelial dysfunction	Yudkin, Atherosclerosis 2000 (72) Kotronen, Liver Int 2011 (67) Juhan-Vague I, Arterioscler Thromb 1993 (69)
Decreased efficacy of the protein C/protein S system	Dyslipidaemia	Mineo, Circ Res 2006 (75) Xie, J Thromb Thrombolysis 2012 (76)

*Number in brackets corresponds to the reference list.

gressively with increasing number of metS components (55). Analysis of clot density in prospective studies is warranted to document the pathogenicity of this haemostasis trait in patients with metS, as stiffer and denser clots were associated with premature cardiovascular disease (56).

IR in macrophages promotes formation of a necrotic core in atherosclerotic plaques by enhancing macrophage apoptosis (57). This is an important event in advanced atherosclerosis because exposure of the necrotic core to circulating blood in the event of plaque rupture can precipitate thrombosis through TF exposure. The blood-borne TF encrypted on the circulating microparticles derived from vascular cells is a marker of vascular injury and a source of procoagulant activity. Evidence indicates that elevated levels of blood-borne or circulating TF has been associated with metS (58) and is a candidate biomarker for future cardiovascular events (59). The elevated TF level may result from various stimulants which accompany metS (60). Among them, hyperinsulinaemia may be of particular relevance. Adipose and circulating TF are potentiated by insulin administration in obese mice (61, 62) and humans (42), respectively. Also leptin and adiponectin both modulate TF expression by monocytes (60). Weight loss significantly reduced circulating plasma TF (63). Despite the important role of TF in initiation of coagulation, the relevance of blood-borne TF for thrombosis in metS deserves to be documented.

In non-diabetic elderly men and women, increased levels of vitamin K-dependent coagulation proteins clustered with dyslipidaemia and inflammation whereas they were not related to anthropometric parameters or arterial pressure or glucidic metabolism (64). These results may be in favour of a potentiation of hepatic synthesis of vitamin K-dependent proteins during metS. Liver steatosis could play an important role in this process. Liver fat is highly significantly and linearly correlated with all components of metS independent of obesity. In agreement, a strong relationship has been reported between circulating levels of vitamin K-dependent proteins and that of the hepatic enzyme gamma glutamyl transferase (65). A proteomic analysis recently demonstrated key changes in protein expression between control subjects and patients with different stages of fatty liver, including an increase in fibrinogen and prothrombin levels (66).

Factors XI and XII were consistently elevated in subjects with non-alcoholic fatty liver as compared to those without disease independently of age, gender and BMI (67). Although the increases were relatively small; the combined effect of these factors could be of clinical significance.

Fibrinogen levels (68, 69) and factor VIII (69-71) associate strongly with metS cluster. These elevations have to be related to the inflammatory state that accompanies metS (72).

Dyslipidaemia may directly affect activation of coagulation factors. Very low-density lipoprotein (VLDL) produced in excess during metS supports activation of factor VII by the Xa/Va (73, 74), and HDL, the levels of which are diminished during the metS, attenuates the expression of TF and downregulates thrombin generation via the enhancement of the anticoagulant protein C pathway (75). Free fatty acids also inhibit the protein C system in endothelial cells which may be a mechanism for the prothrombotic state in metS (76).Therefore the dyslipidaemia which accompanies metS could be involved in the thrombotic risk by increasing thrombin generation.

Measurement of endogenous thrombin potential (ETP) is a more accurate index of a hypercoagulable phenotype than traditional coagulation tests that only reflect the initial formation of thrombin. Several studies have reported a relationship between ETP and the incidence of venous thrombosis (VT) and more recently of acute ischaemic stroke (77). We recently observed that ETP was significantly increased after high fat diet (HFD) in rats and correlated with liver weight but not with BMI or indices of IR indicating that coagulation changes observed during the metS may reflect HFD-induced liver alterations (78).

Hypofibrinolysis

Subjects with metS had prolonged clot lysis times (CLT) compared with those without metS, partly due to increased circulating levels of plasminogen activator inhibitor 1 (PAI-1) which is the most important and visible change of the haemostatic system in the metS (79).

Increased concentration of PAI-1 leads to impairment of the removal of thrombi from the vascular system and may influence the development of atherosclerotic lesions as well (80). In large epidemiological studies, elevated plasma levels of PAI-1 proved to be predictors of myocardial infarction (81). Remarkably, the predictive ability of PAI-1 disappears after adjustment for markers of the metS (81). These results suggest that the presence of central obesity and IR is a prerequisite for the increased PAI-1 levels in patients at risk of atherothrombosis and have led to the proposal that increased PAI- 1 level can be considered as a true component of the metS (82). The increase in plasma PAI-1 levels associated with abdominal obesity may be attributed to PAI-1 production by ectopic ATs (83-87) and fatty liver (88, 89). Tissue expression of PAI-1 is not constitutive but mainly inducible. Many inducers of PAI-1 synthesis during metS have been identified that may exert their effects locally or more remotely in different cell types as endothelial cells, hepatocytes, Ito cells, fibroblasts, adipocytes etc.

Circulating PAI-1 levels predict development of type 2 diabetes (90-93) and metS (94, 95), suggesting that PAI-1 may be causally related to deterioration of metabolic homeostasis. Fat accumulation was prevented in mice lacking PAI-1 in both a nutritionally induced (96, 97) and a genetic (98) murine model of obesity. Results obtained by our group (99-101) followed this direction, showing an effect of pharmacological inhibition of PAI-1 on weight gain and on insulin sensitivity.

In addition, PAI-1 deficiency may exert beneficial effects through improved insulin sensitivity in adipocytes (102, 103). PAI-1 is stabilised by binding to vitronectin. PAI-1 may inhibit preadipocytes attachment to vitronectin (104). In addition PAI-1-mediated inhibition of insulin signalling occurs through its direct interaction with vitronectin (103). More recently we demonstrated that PAI-1 inhibits furin-dependent processing of the insulin receptor, which reduces its phosphorylation and, hence, subsequent

Akt phosphorylation. Consequently, through furin inhibition, PAI-1 impairs the cellular insulin response, which could contribute to development of IR (105).

Findings suggest that targeted PAI-1 overexpression in macrophages and adipocytes impairs AT growth in mice (106), which agrees with the described inhibitory effect of PAI-1 on murine adipocyte differentiation (102) not reproduced in other study (107). This finding must be interpreted in connection with the multiple facets of PAI-1, which render it a serpin that acts locally at various sites and perhaps systemically through endocrine effects. The effects of PAI-1 on adipogenesis may be concentration dependent. This has been well documented for angiogenesis which contributes to adipose tissue development. At nanomolar concentration PAI-1 promoted angiogenesis through its anti-proteolytic activity whereas micromolar concentrations were anti-angiogenic attributed to its vitronectin binding function (108). Interestingly, old transgenic mice overexpressing PAI-1 and maintained on standard fat diet exhibit significantly higher insulinaemia and a tendency toward higher triglyceride levels, despite lower body fat (106). These data are not inconsistent with those obtained in PAI-1-deficient mice and indicate that PAI-1 overexpression might worsen the metabolic profile. This requires confirmation, because this deleterious effect was not found in younger transgenic mice fed a HFD (106).

Endothelial dysfunction

In healthy conditions insulin promotes glucose disposal and stimulates the endothelial production of NO, which in turn, through NO-dependent increases in blood flow to skeletal muscle, may account for 25% to 40% of the increase in glucose uptake in response to insulin stimulation (109). A physiologic increment in plasma insulin concentration particularly increases microvascular blood volume, consistent with a mechanism of capillary recruitment (110) that may be more important for glucose tolerance than the insulin effect on total blood flow. Capillary recruitment not only increases muscle glucose uptake but also contributes to the increased delivery of insulin to muscle and increases the endothelial surface available for transendothelial insulin transport.

IR is characterised by pathway-specific impairment in phosphatidylinositol 3-kinase-dependent signalling, which in endothelium, may cause imbalance between production of NO and secretion of endothelin-1, leading to decreased blood flow and capillary recruitment, which worsens IR (111-113). In addition to a modulation of vasoactive properties, decrease in NO production may increase vascular permeability and smooth muscle proliferation (114). Conditional knockout of the insulin receptor in endothelial cells causes a two- to three-fold increase in the atherosclerotic lesion size in apolipoprotein E–null mice that has been attributed to insulin action directly on endothelial cells and not to a difference in systemic insulin sensitivity (115).

In parallel with inadequate vasodilatation, in obesity, endothelial cells take a proinflammatory phenotype with increased expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), E selectin, a release of microparticles (116, 117) and an increased synthesis and release of the adhesive protein von Willebrand Factor (VWF) which levels correlated with parameters of the metS (69, 70) and inflammatory parameters (69, 118, 119). These endothelial disorders may arise at a very early age in obese children (120). In agreement, the accelerated atherosclerosis in mice with endothelial cell insulin receptor knockout is preceded by a dramatic increase in leukocyte rolling and adhesion to endothelium and an increase in expression of VCAM-1 (115). Decreased endothelium-derived NO partly explained these effects and it is likely that other mechanisms perhaps through the nuclear factor forkhead box O1 ($FoxO_1$/FKHR) accounts for these properties. Transcriptional activity of $FoxO_1$ is suppressed by insulin (121) and $FoxO_1$ upregulates VCAM-1 expression (122). Overall it may be proposed that that loss of insulin signalling promotes atherosclerosis development. In association with insulin resistance, glucotoxicity, lipotoxicity, inflammation, oxidative stress may all participate to the endothelium dysfunction that accompanies the metS.

Thrombosis

The metS has been recognised as a risk factor of atherothrombotic diseases (123-126). A meta-analysis of > 950,000 patients found a two-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality with the presence of the metS (127).

Obesity and metS are often associated. Some studies have tried to evaluate the specific contribution of obesity and metS. In the community-based Uppsala Longitudinal Study of Adult Men (ULSAM), patients were categorised as normal weight, overweight or obese with or without metS. During follow-up (median 30 years), 788 participants died, and 681 developed cardiovascular disease (composite endpoints). During more than 30 years of follow-up, subjects with metS had increased risk for cardiovascular events and total death regardless of BMI status (128). The recent meta-analysis of Coutinho et al. illustrates that central obesity but not BMI is directly associated with cardiovascular mortality. In this study, the authors searched OVID/Medline, EMBASE, CENTRAL, and Web of Science from 1980 to 2008 and asked experts in the field for unpublished data meeting inclusion criteria. The final sample consisted of 15,923 subjects. There were 5,696 deaths after a median follow-up of 2.3 years. Central obesity was associated with mortality (hazard ratio [HR]: 1.70, 95% confidence interval [CI]: 1.58 to 1.83), whereas BMI was inversely associated with mortality (HR: 0.64, 95% CI: 0.59 to 0.69). Importantly central obesity was also associated with higher mortality in the subset of subjects with normal BMI and BMI ≥30 kg/m^2 (129). These results underline that BMI is not truly representative of total fat distribution and may explain the inverse relationship observed between obesity and cardiovascular mortality, the so called "obesity paradox" observed in some studies (130) that used almost exclusively the BMI as an index of obesity. In agreement with this, low fitness and central obesity measured by waist to hip ratio were independently and cumulatively associated with increased mortality in

coronary artery disease patients attending cardiac rehabilitation in the Mayo Clinic (131). On the contrary, obese subjects did not have a significantly different mortality as compared with the reference group of normal weight-high fitness subjects (131).

Since metS corresponds to the association of several individual risk factors some studies investigate whether or not the prognostic significance of the metS exceeds the risk associated with the sum of its individual components. A meta-analysis investigated the association of metS and its components with progression of coronary atherosclerosis. After adjusting for its individual components, metS was no longer an independent predictor of plaque progession (132). The INTERHEART study (n = 26,903) involving 52 countries examined the risk of acute myocardial infarction (MI) conferred by the metS and its individual factors in multiple ethnic populations. MetS was associated with an increased risk of MI, both using the WHO (odds ratio [OR]: 2.69; 95% CI: 2.45 to 2.95) and the IDF (OR: 2.20; 95% CI: 2.03 to 2.38) definitions (133).

Given the evidence of hypercoagulability, hypofibrinolysis and endothelial dysfunction in carriers of the metS there is a rationale to hypothesise that the metS may also predispose patients to develop VT (134) (►Table 3). Most of the haemostatic defects observed in metS have been associated with VT. Reduced plasma fibrinolytic potential, a constant feature of metS, is a risk factor for venous thrombosis (135) that was found to be explained by elevated plasma levels of PAI-1 (136). Several lines of research indicate that platelets play a determining role in VT though they have historically been ignored in this pathology. Activated platelets are important catalysts of both intrinsic and extrinsic thrombin generation and thus fibrin production (137). The platelet collagen receptor GPVI, whose membrane expression is increased in type 2 diabetes (138), was recently identified in a genome-wide association study that searched for novel risk factors for VT (139). Finally the use of aspirin may decrease the risk of first and recurrent VT (140). Also VT patients more frequently have impaired flow-mediated dila-

Table 3: Association between venous thrombosis and visceral obesity or metabolic syndrome.

Type of study (n)	Analysed parameters	Adjusted HR (95%CI)	Related references*
Case/Control (146/150)	Abdominal obesity	First VT episode 5.7 (3.4–9.6)	Vayà, Metab Syndr Relat Disord 2011 (155)
Case/ Control (323/868)	Abdominal obesity : Waist circumference > 102 cm for men and > 88 cm for women	Early-onset idiopathic VT 2.715 (1.95–3.715)	Di Minno, Thromb Res 2011 (160)
Registry, 3 months follow up after total knee replacement (1460)	Metabolic syndrome defined as hypertension, hypercholesterolaemia, diabetes, and obesity	Symptomatic VT 3.2 (1–15.4)	Gandhi, J Rheumatol 2009 (164)
Prospective study (6170) average 10.8 years follow up	Abdominal obesity : Waist circumference >102 cm for men and > 88 cm for women	Incident VT 2.03 (1.49–2.75)	Borch, J Thromb Haemost 2009 (166)
Prospective study (20374) average 12.5 years follow up	Abdominal obesity : Waist circumference >102 cm for men and > 88 cm for women	Incident VT Men : 2.10 (1.51– 2.93) Women : 1.70 (1.24– 2.34)	Steffen, J Thromb Haemost 2009 (165)
Prospective study (5522) 5 years median follow up	Features of the metabolic syndrome (0–1 vs 4 features)	Incident VT 1.26 (0.59–2.69)	Ray, QJM 2007 (157)
Case/Control (84/94)	Metabolic syndrome according to 2001 NCEP guidelines	Idiopathic VT 2.14 (1.12–4.08)	Dentali, Haematologica 2007 (161)
Case/Control (86/95)	Metabolic syndrome according to 2001 NCEP guidelines	VT in acute cardiac conditions 2.38(1.64–3.12)	Ambrosetti, Thromb Res 2007 (162)
Case/Control (116/129)	Metabolic syndrome according to 2005 NCEP ATP III criteria	Recurrent VT 2.2 (1.1–4.3)	Ay, Haematologica 2007(163)
Case/Control (93/107)	Metabolic syndrome according to 2001 NCEP guidelines	First VT episode 1.94 (1.04–3.63)	Ageno, J Thromb Haemost 2006 (159)
Necropsy study (23796)	Abdominal subcutaneous fat measured after incision	Pulmonary embolism 1.28 (1.07–1.53)	Ogren, J Intern Med 2005 (158)
Prospective study (850 men)	Abdominal obesity : waist circumference > 100 cm	VT Highest decile of waist circumference : 3.92 (2.10–7.29)	Hansson, Arch Intern Med 1999(156)

*Number in brackets corresponds to the reference list.

tation, recognised as an indicator of arterial endothelial dysfunction (141) and exhibited increased thrombin generation (142).

Apart from haemostasis parameters some individual components of the metS have been associated with VT mainly dyslipoproteinaemia involving high TG levels, low HDL particles, small LDL particles (143-146). A meta-analysis assessed the association between cardiometabolic risk factors and VT (147). A total of 63,552 subjects met the inclusion criteria. Compared with control

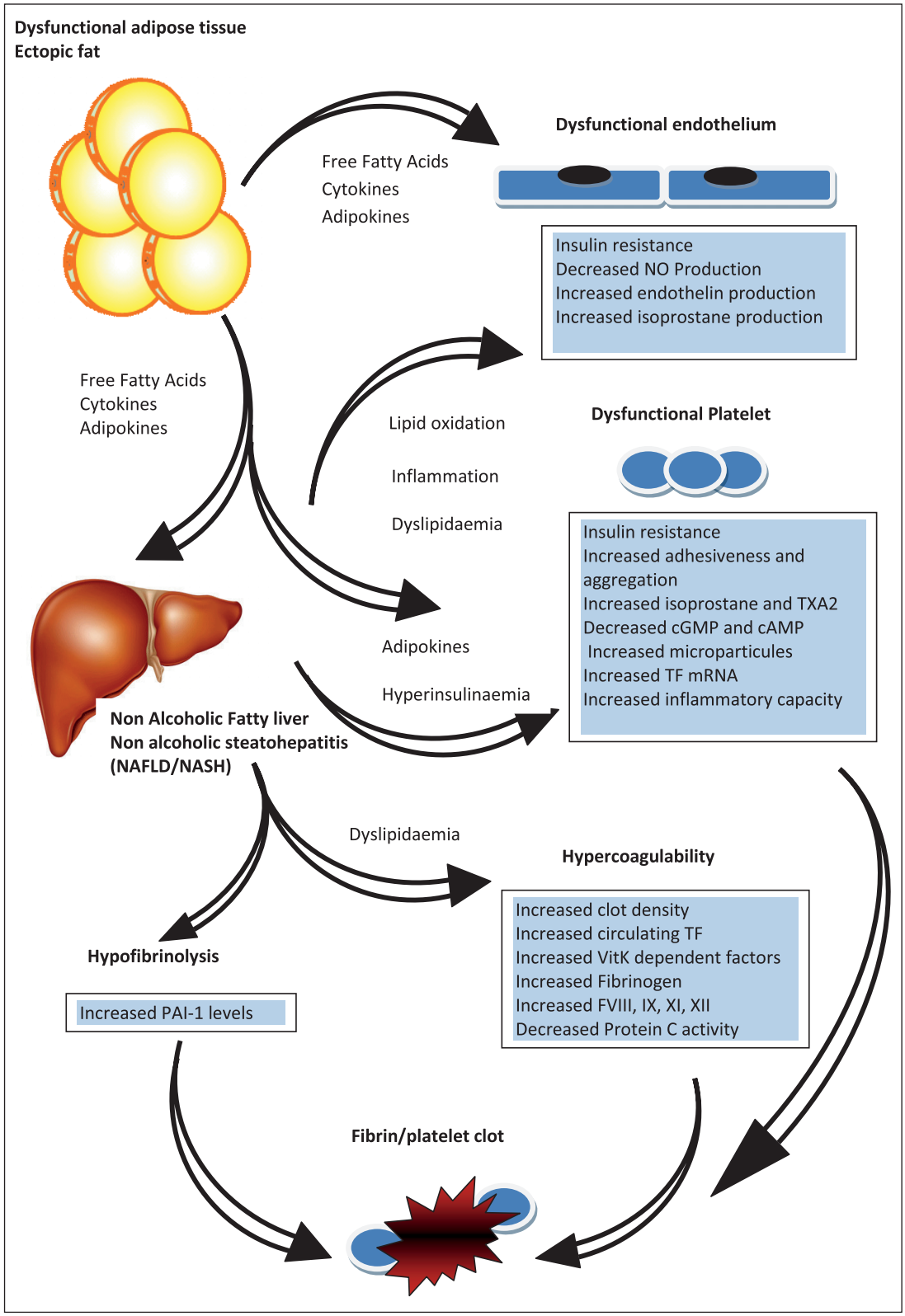

Figure 1: Schematic representation of detrimental mechanisms during visceral obesity with respect to haemostasis.

subjects the risk of VT was 2.33 for obesity, 1.42 for diabetes mellitus. HDL cholesterol was inversely and consistently correlated with VT and triglycerides were on average 21 mg/dl higher in patients with VT than in controls. Despite these results the community based observational cohort study, the PREVEND study, does not show any association between both apolipoproteins or the classical lipoproteins and VT risk (148).

Only one study investigated whether IR is a risk factor for VT. In the large PREVEND prospective community-based observational cohort study high HOMA-IR and fasting insulin were associated with increased risk of VTE after adjustment for traditional cardiovascular risk factors, C-reactive protein (CRP) and markers of endothelial dysfunction but this association disappeared after adjustment for BMI (149).

Obesity is recognised as a strong and independent predictor for VT. In the large Copenhagen city heart study, extreme BMI ≥ 35 was found significantly associated to VT (HR=2.10, 95%CI = 1.39 to 3.16). In this study HDL, triglycerides, diabetes mellitus was not independently associated with VT (150) but the contribution of visceral/central fat, a key contributor to metS, has not been fully evaluated. Central obesity is associated with raised intra-abdominal pressure and reduced venous blood flow velocity, which may render blood more susceptible to thrombosis (151, 152). A recent study showed that lower limb venous flow parameters differed significantly between healthy obese and non-obese subjects, suggesting a mechanical role of abdominal AT, potentially leading to elevated risk of VT (153). In a small case control study VT was considered as strongly associated with thickness of epicardial fat (154), a surrogate marker of visceral fat. In a Mediterranean population, abdominal obesity was the only factor that remained statistically associated with higher VT risk (155). The prospective study of men born in 1913 showed that a waist circumference of more than 100 cm had a higher incidence of VT than men with a waist circumference less than 100 cm leading to an adjusted relative risk of 3.92 (156). In 2007, Ray et al. (157) investigated the association between VT and features of the metS in a prospective cohort of adults with cardiovascular disease or diabetes and additional risk factor. This cohort, derived from the HOPE-2 randomised clinical trial, enrolled 5,522 subjects older than 55 years and followed for a median of five years. Again elevated waist circumference was significantly associated with VT. In a very large study, including 23,796 autopsies, subcutaneous fat (abdominal and thoracic) was strongly and independently associated with pulmonary embolism (158). Small case-control studies have investigated the association between metS defined according to NCEP-ATPIII criteria and the occurrence of VT. The metS was significantly more common in patients with idiopathic VT than in controls (159-161) even in acute cardiac conditions (162). In the study of Ay et al. (163) patients with recurrent VT had significantly higher BMI, waist to hip ratio and triglyceride levels than controls. MetS was diagnosed in 35% of patients and 20% of controls leading to an adjusted OR of 2.1. Interestingly, it was not the presence of a single component but rather the constellation of multiple components that was crucial in this association. A provoked VT was also more common in patients suffering metS (164). In the large LITE study, metS defined using ATP III guidelines was associated with risk of total and idiopathic VT among men, but not women. The association was largely attributable to central obesity with no additional contribution of the other metS components (165). Borch et al. also confirmed the pivotal role of central obesity in VT among the features of metS. The risk of VT increased with the number of components of metS (166). Abdominal obesity was the only component significantly associated with VT in multivariable analysis including age, gender, and the individual components of the syndrome (HR 2.03; 95% CI 1.49-2.75). When abdominal obesity was omitted as a diagnostic criterion, none of the other components, alone or in cluster, was associated with increased risk of VT. Overall most of the literature results indicate that the effect of metS on VT risk may be related to visceral fat.

Conclusion

Central obesity is accompanied by important changes in the haemostatic system and the vascular bed that may favour the development of thrombosis. A relevant role can be recognised for hyperactivity of platelets and hypercoagulability that favour platelet and fibrin deposits, and hypofibrinolysis due to the PAI-1 excess that prevents fibrin elimination. In addition, several other modifications can interplay with haemostasis leading to a situation associated with increased thrombosis (►Figure 1). Epidemiological evidence has established the contribution of central obesity to arterial disease; the literature results also indicate an effect of central obesity on VT risk. Therapy targeting reduction of visceral obesity and its associated disorders: liver steatosis, lipid abnormalities, particularly low HDL cholesterol and high triglycerides levels, may help to control the thrombotic process and promote cardiovascular health.

Conflicts of interest
None declared.

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