Review Article

Metabolic syndrome, haemostasis and thrombosis

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Summary

The metabolic syndrome (metS), a concurrence of abdominal fat, disturbed glucose and insulin metabolism, dyslipidemia, and hypertension has been strongly associated not only with subsequent development of type 2 diabetes but also with atherothrombosis. The physiopathology of this association is complex. The metS affects the thrombogenicity of circulating blood. Apart from its effect on platelets, a procoagulant and hypofibrinolytic state has been identified; mainly the result of the inflammatory state, dyslipidemia, and liver fat accumulation that accompany the MetS. Among haemostasis disturbances, the strong rise in the inhibitor of plasminogen activator type 1 plasma level is the most documented abnormality implicating the participation of the oxidative stress and inflammatory state developed during the metS. Endothelial dysfunction is also a central feature. Moreover, secretion products of fat tissues (adipokines) are now thought to have direct modulating effects on the vascular and the circulating cells. In support of these data, the metS, may predispose not only to atherosclerosis but also to venous thrombosis.

Keywords

Haemostasis, metabolic syndrome, visceral obesity, platelet, coagulation, fibrinolysis, endothelial dysfunction

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Introduction

The metabolic syndrome (metS), is a clinical entity of substantial heterogenous traits represented by the co-occurence of abdominal fat, impaired glucose tolerance, dyslipidemia (high triglycerides and low high-density lipoprotein [HDL] cholesterol levels) and hypertension. The conference on metS definition of the American Heart Association (1) underlined two additional components that are a proinflammatory and a prothrombotic states and confirmed cardio vascular disease and type 2 diabetes as major clinical outcomes of metS.

Although the prevalence of the components of the metS is increased in obesity (2), it is important to notice that not all obese subjects develop metS, and even non-obese individuals can carry metS.

Pathophysiology of this syndrome mainly involved three ways of thinking: (i) central obesity also known as ectopic fat disease, (ii) insulin resistance, and (iii) a constellation of independent factors (e.g. molecules of hepatic, vascular, and adipose origin) that mediate specific components of the syndrome.

In this review we describe the relationships between the components of the metS and alterations in hemostasis that may predispose to both arterial and venous thrombosis.

Metabolic syndrome and platelet hyperactivity

Increased platelet response is seen in individuals with the metS (3–8) supported by the main features of metS: insulin resistance, dyslipidemia, products of adipose tissue (adipokines) and inflammation.

Insulin resistance refers to resistance to the metabolic and vascular activities of insulin in a variety of cells, including mainly hepatocytes, muscle cells, and adipocytes. Insulin possesses antiplatelet properties (6). Attenuation of platelet response in insulin resistant patients have been connected to a reduced platelet sensitivity to insulin (9). Loss of platelet inhibition by insulin in patients with insulin resistance may be related to loss of insulin-mediated suppression of ADP-induced P2y12 signaling as well as decreased P2y12 inhibition by receptor antagonists (10). This may explain the association between diabetes and resistance to the antiplatelet effects of clopidogrel (11). Other mechanisms have been documented to explain platelet hyperactivity as an elevated cytosolic Ca(2+) and the increase of oxidative stress, which elicits isoprostane production from arachidonic acid (12).

Hypertriglyceridemia and increased concentration of free fatty acids exert a proaggregating effect *in vitro* (13). Hypo-

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HDLaemia also influences platelet aggregation, possibly because HDL opposes the activation properties of low-density lipoprotein (LDL) on platelets (14). The exact mechanisms of these effects are not clearly elucidated.

Adipokines may directly influence platelet function. Plasma leptin reflects mainly adipose tissue mass, and a strong association was found between circulating leptin and insulin resistance (15). Leptin receptors have been identified in the cardiovascular system (16) as well as in platelets. Leptin potentiates the normal response of platelets to adenosine diphosphate and thrombin (17–19). However, four-day leptin infusion only slightly increases platelet aggregation in healthy volunteers (20). Moreover carriers of leptin deficiency exhibited increased platelet aggregation relative to controls, and incubation *in vitro* with leptin did not increase up platelet aggregation (21). Thus, one may argue that factors other than leptin modulate platelet function in extreme obesity or that obesity is associated with impaired platelet sensitivity to leptin, i.e. leptin resistance resembling the reduced sensitivity of platelets to insulin in insulin resistance (22, 23). This needs to be confirmed *in vivo*. The adipokine, adiponectin, is abundantly present in plasma. Its plasma concentration decreases in obesity, type 2 diabetes, and patients with coronary artery disease. In recent years, a great amount of literature has suggested a close connection between adiponectin and each inherent trademark of the metS (24). Results obtained in adiponectin knockout mice indicate that adiponectin acts as an endogenous antithrombotic factor (25). In-vitro platelet aggregation induced by low concentration of agonists was enhanced in adiponectin knockout mice, and recombinant adiponectin overcame the enhanced platelet aggregation (25). However, addition of adiponectin did not affect either aggregation or adhesion of human platelets; even at supra-physiological concentrations (26). Lastly platelet, may be activated by the low-grade systemic inflammatory state seen in visceral obesity (27).

Pharmacological inhibition of platelet functions is at the center of the treatment of active cardiovascular disease and in the secondary prevention of cardiovascular events. However, there are divergent views, between guidelines, on which patients with type 2 diabetes require aspirin in the primary prevention strategy as well as on the dose of aspirin (28). In addition, there is no data regarding antiplatelet therapy in patients with metS without diabetes despite prognostically important coronary arterial disease in these patients. This high level of uncertainty will deserve to be precised in randomized clinical trials taking into account the lower potency of antiplatelet therapy described in patients with diabetes (28, 29) and insulin-resistant obesity (30).

Metabolic syndrome and hypercoagulability

Plasma from subjects with the metS formed denser clots compared with subjects free from metS. In addition clot density increased progressively with increasing number of metS components (31). 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 (32).

Tissue factor (TF), the key initiator of coagulation is widely expressed in atherosclerotic plaques and found in macrophages, smooth muscle cells, extracellular matrix and acellular lipid-rich core. 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 (33) and is a candidate biomarker for future cardiovascular events (34). The elevated TF level may result from various stimulants which accompany the metS such as C-reactive protein, oxidized LDL, tumor growth factor (TGF) beta, angiotensin II, hyperglycemia, and adipocytokines (35). Among them, hyperinsulinemia may be of particular relevance. Adipose and circulating TF are potentiated by insulin administration in obese mice (36, 37) and humans (38), respectively. 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 dyslipidemia and inflammation, whereas they were not related to anthropometric parameters or arterial pressure nor glucidic metabolism (39). These results may be in favour of a potentiation of hepatic synthesis of vitamin K-dependent proteins during the metS. Liver steatosis could play an important role in this process. Liver fat is highly significantly and linearly correlated with all components of the metS, independent of obesity. Overproduction of coagulation factors in addition to glucose and very low-density lipoprotein (VLDL) by the fatty liver could contribute to the excess risk of cardiovascular disease associated with the metS. 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 (40).

Fibrinogen levels associates importantly with metS cluster (41) as factor VIII (FVIII) (42, 43). These elevations has to be brought closer to the inflammatory state that accompanies the metS. Indeed, FVIII circulates as an inactive procofactor in complex with the acute-phase protein von Willebrand factor, which slows down FVIII elimination. The increase in IL-6 levels that accompagnies the metS may be responsible for the slight increase in hepatic synthesis of fibrinogen (44, 45).

It has been reported that dyslipidemia may directly affect activation of coagulation factors. VLDL produced in excess during the metS supports activation of factor VII by the Xa/Va (46, 47) and HDL that levels are diminished during the metS, attenuate the expression of TF and downregulates thrombin generation via the enhancement of the anticoagulant protein C pathway (48). Therefore, the hypoHDLaemia which accompanies the metS could be involved in the thrombotic risk by increasing thrombin generation.

Metabolic syndrome and hypofibrinolysis

Subjects with metS had prolonged clot lysis times compared with those without metS (31), partly due to increased circulating levels of plaminogen activator inhibitor 1 (PAI-1) that is the most important and visible change of the haemostatic system in the metS (49).

Increased concentration of PAI-1 leads to impairment of the removal of thrombi from the vascular system (50) and may in-

fluence the development of atherosclerotic lesions as well (51). In large epidemiological studies, elevated plasma levels of PAI-1 proved to be predictors of myocardial infarction (49). Remarkably, the predictive ability of PAI-1 disappears after adjustment for markers of the metS (52). These results suggest that the presence of abdominal obesity and insulin resistance 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 (53).

The increase in plasma PAI-1 levels associated with abdominal obesity may be attributed to PAI-1 production by ectopic adipose tissues (54–58) and fatty liver (59, 60). Overall these findings suggest that circulating PAI-1 levels reflect fat redistribution and may be considered a biomarker of ectopic fat storage disease, a feature of central obesity.

Tissue expression of PAI-1 is not constitutive but mainly inducible. Many inducers of PAI-1 synthesis during visceral obesity have been identified that may exert their effect locally or more remotely (49). Establishment of inflammation or oxidative stress at the macrophage level as fundamental precursors of PAI-1 overexpression in metS is tempting.

Circulating PAI-1 levels predict development of type 2 diabetes (61–64) and more recently metS (65), suggesting that PAI-1 may be causally related to deterioration of metabolic homeostasis. Three groups found that fat accumulation was prevented in mice lacking PAI-1 in both a nutritionally induced (66, 67) and a genetic (68) murine model of obesity. Results obtained by our group (69–71) 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 (72). This effect may be mediated through the ability of PAI-1 to impair the cooperation between integrin $\alpha_v\beta_3$ and insulin signalling (73, 74) or to block the deleterious effect of tumor necrosis factor (TNF) on insulin sensitivity (72).

Findings suggest that targeted PAI-1 overexpression in macrophages and adipocytes impairs adipose tissue growth in mice (75), which agrees with the recently described inhibitory effect of PAI-1 on murine adipocyte differentiation (72) not reproduced by another study (76). This finding may, at first glance, appear to be at odds with that obtained in PAI-1-deficient mice, but it 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. Interestingly, old transgenic mice overexpressing PAI-1 and maintained on a standard fat diet exhibit significantly higher insulinaemia and a tendency toward higher triglyceride levels, despite lower body fat (71). 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 diet high in fat (75).

Overall, these data support the concept that PAI inhibition (77) has the potential to reduce obesity and improve insulin sensitivity, and may represent a new therapeutic target. This requires confirmation in different experimental models, and the mechanisms involved should be precisely defined.

Metabolic syndrome and endothelial dysfunction

In healthy conditions insulin promotes glucose disposal and stimulates the endothelial production of nitric oxide (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 (78). A physiologic increment in plasma insulin concentration particularly increases microvascular blood volume, consistent with a mechanism of capillary recruitment (79).

Insulin resistance is characterized 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, which worsens insulin resistance (80–82). Experimental inhibition of phosphatidylinositol 3-kinase with wortmannin not only blocked the ability of insulin to stimulate increased expression of endothelial NO synthase but also increased expression of vascular cellular adhesion molecules-1 and E-selectin, and increased rolling interactions of monocytes with endothelial cells, showing that inhibition of the metabolic branch of insulin signalling leads to an enhanced atherogenic action of insulin in endothelial cells (83).

In parallel with inadequate vasodilatation, in obesity endothelial cells take a proinflammatory phenotype with increased expression of VCAM1, ICAM1, E selectin, a release of microparticles (84) and shedding products, and an increased synthesis and release of the adhesive protein von Willebrand factor which levels correlated with parameters of the metS (42, 85) and inflammatory parameters (42, 86–88). These endothelial disorders may arise at a very early age in obese children (89).

Metabolic syndrome and thrombosis

The metS is a well recognized risk factor of acute cardiovascular disease (90–93). Given the evidence of an hypercoagulability, hypofibrinolysis and endothelial dysfunction in the carriers of the metS there is a rationale to hypothesize that the metS may also predispose patients to develop venous thromboembolism (VTE) (94). In addition VTE was found to be associated with atherosclerosis more frequently than expected (95) leading to several hypotheses among which that of the metS as a common antecedent.

Some individual components of the metabolic syndrome have been associated with VTE mainly dyslipoproteinemia involving high triglyceride (TG) levels, low HDL particles and small LDL particles (96–99). A recent metanalysis assessed the association between cardiovascular risk factors and VTE (100). A total of 63,552 subjects met the inclusion criteria. Compared with control subjects the risk of VTE was 2.33 for obesity and 1.42 for diabetes mellitus. HDL cholesterol was inversely and consistently correlated with VTE, and triglycerides were on average 21 mg/dl higher in patients with VTE than in controls.

Few data have been provided on visceral obesity or the metS considered as a whole. The prospective study of men born in 1913 showed that men with a waist circumference of more than 100 cm had a higher cumulative incidence of VTE than men with a waist circumference less than 100 cm leading to a adjusted

relative risk of 3.92 (101). More recently Ray et al. (102) investigated the association between VTE 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 randomized 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 VTE.

Two recent small size case-control studies have investigated the association between the metS defined according to NCEP-ATPIII criteria (103) and the occurrence of VTE. In the first study (96) the metS was significantly more common in patients with idiopathic VTE than in controls in uni- and multivariate analysis. Ay et al. (104) found that patients with reccurent VTE had significantly higher body mass index, waist-to-hip ratio and triglyceride levels than controls. The metS was diagnosed in 35% of patients and 20% of controls leading to an adjusted odds ratio of 2.1. Interestingly it was not the presence of a single component but rather the constellation of multiple components that is crucial in this association.

Conclusion

The metS is accompanied by important changes in the haemostatic system that may favour the development of thrombosis. Hyperactivity of platelets and hypercoagulability favour platelet and fibrin deposits, and hypofibrinolysis due to the PAI-1 excess prevents their elimination. The increased PAI-1 expression that accompanies abdominal obesity is the most documented abnormality associated with the metS. As PAI-1 could also be directly involved in the physiopathology of obesity, it could represent an original target for preventing both the thrombotic and metabolic risks. Whereas strong epidemiological evidences have established the contribution of metS to cardiovascular disease, better illustration is needed to establish whether metS is a relevant risk factor for VTE.

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