

## SHORT COMMUNICATION

**Prothrombotic state in metabolic syndrome**

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Metabolic syndrome (MS), also known as insulin resistance syndrome, is defined as a cluster of several cardiovascular risk factors in an individual patient, including impaired glucose tolerance or diabetes, hypertension, dyslipidaemia, and visceral obesity. Several studies have demonstrated that this syndrome strongly predicts cardiovascular disease. Recently, a close association of MS with haemostatic abnormalities has been reported. These patients therefore may tend toward a prothrombotic state. Prothrombotic state is considered to be one of the components of MS, which takes part in the development of atherothrombotic complications.

The mechanism of the prothrombotic state in MS is multifactorial. The dysregulation of haemostasis in MS involves endothelial dysfunction, platelet hyperactivity, hypercoagulability and hypofibrinolysis.

The main haemostatic abnormality in relation to MS is the increase in the plasminogen activator inhibitor type 1 (PAI-1) associated with **hypofibrinolysis**. PAI-1 is the most potent inhibitor of fibrinolysis *in vivo*. It is considered to be the core feature of MS, closely associated with its components. PAI-1 is synthesized in many tissues, mainly in adipose tissue and vascular endothelial cells. In subjects with MS, the main production site is the increased adipose tissue mass. Multivariate analysis showed a clear relationship between plasma PAI-1 and body mass index, suggesting that obesity is the main determinant of plasma PAI-1 concentrations. High plasma concentrations of PAI-1 may play a role in thrombus formation, causing cardiovascular events. In patients with diabetes mellitus type 2, fibrinolysis can be probably impaired also via elevated concentrations of thrombin-activatable fibrinolysis inhibitor (TAFI). TAFI is thought to be another potent inhibitor of fibrinolysis, but PAI-1 appears to be a more important determinant of fibrinolytic activity. It could be suggested that TAFI may be also a component of MS. In contrast to PAI-1, TAFI is produced exclusively by liver.

The most important coagulation abnormality related to MS is the increased concentration of fibrinogen, causing *hypercoagulability*. Plasma fibrinogen level is a marker of inflammation

and it can be higher especially in diabetic patients. The increase in plasma fibrinogen is considered to be one of the predictors of coronary artery disease.

**Platelet hyperactivity** reported in patients with MS appears to be another haemostasis disorder involved in the pathogenesis of atherothrombotic vascular complications. Atherogenesis is now considered to be a chronic inflammatory process in which activated platelets aggregate with leukocytes, release proinflammatory cytokines, chemokines and growth regulatory molecules, resulting in endothelial activation up to endothelial damage. As a response to vascular injury, platelets are deposited at denuded endothelium, playing a role in the development of atherothrombosis. For example, the increased platelet activity may be observed already in the early stages of essential hypertension. In comparison with sex- and age-matched healthy subjects, we found a significant increase of platelet aggregation (both spontaneous and adrenaline-induced) as well as plasma  $\beta$ -thromboglobulin (a marker of platelet activation *in vivo*) in untreated hypertensives (1). It has been shown that also the circulating P-selectin, another marker of platelet activation is higher in diabetic patients than in non-diabetic subjects.

It is documented that MS and especially diabetes mellitus type 2 is associated with diffuse *endothelial dysfunction and/or damage*. This is accompanied by the increase in several soluble endothelial markers in plasma such as von Willebrand factor (vWF), thrombomodulin (TM), but also tissue-type plasminogen activator (t-PA) antigen, and PAI-1 activity.

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The results of our previous study demonstrate an increase in both plasma vWF and TM in patients in early stages of essential hypertension when compared to healthy subjects (1).

More recent studies have shown that vWF plasma levels are elevated in the insulin resistance syndrome, although these observations have been overshadowed by the even stronger association between insulin resistance, PAI-1 and fibrinogen levels. However, in patients presenting with states of insulin resistance such as diabetes mellitus type 2 or impaired glucose tolerance, this elevation of vWF was usually smaller than the one associated with microalbuminuria. In the Framingham Offspring study, plasma vWF levels were associated with fasting insulinaemia, a marker of insulin resistance. Insulin resistance and/or obesity are associated with increased production of inflammatory cytokines, suggesting that insulin resistance may increase plasma vWF levels via chronic, low-grade inflammation. Diabetes mellitus and insulin resistance are also associated with a state of chronic oxidative stress. Thus, impaired NO production, inflammation and increased oxidative stress (which are all interrelated) may contribute to the association between insulin resistance and elevated vWF plasma levels.

Many studies have investigated the association between vWF plasma levels and the subsequent risk of cardiovascular disease. Several population studies have described a weak association between plasma vWF and the risk of coronary heart disease (CHD). Current data indicate that plasma vWF levels are at best a weak predictor of cardiovascular disease in the general population. A more convincing association between vWF levels and cardiovascular risk is observed in high-risk populations. Diabetes may represent a high-risk population in which vWF levels are of particular interest. It appears that while the association between vWF levels and CHD in the general population is weak, this association becomes much stronger and independent of inflamma-

tory markers in high-risk populations, in which vWF levels are elevated in a large proportion of patients. In high-risk patients with diabetes and/or pre-existing atherosclerosis, vWF appears to be a more promising risk marker for CHD and death (2).

Some authors have demonstrated an increase in tissue factor pathway inhibitor (TFPI) activity in patients with diabetes. This seems to be particularly true in patients with diabetes and microalbuminuria. Because TFPI is mainly produced by and bound to the vascular endothelium, these data suggest that plasma TFPI level may also reflect the endothelial function.

The association among MS, haemostatic system and endothelial function should be examined in further studies not only for identification of the pathogenesis of cardiovascular events but also for the better medical management of patients with MS. Weight loss due to life-style modifications such as low-caloric diet, physical activity, and adequate pharmacologic interventions influencing simultaneously single components of the MS (anti-hypertensive, antidiabetic, hypolipaeamic, and antithrombotic agents) are effective methods to decrease the impact of prothrombotic state. A complex treatment of prothrombotic state in MS can prevent the development of atherothrombosis and its clinical manifestations (3).

## References

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