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The Metabolic Syndrome And The Risk Of Thrombosis

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The metabolic syndrome is a cluster of risk factors for atherosclerosis, including abdominal obesity, hypertension, insulin resistance, and dyslipidemia with high triglycerides and low HDL cholesterol.¹ This syndrome has recently been included in the International Classification of Diseases,² but there is still no clear consensus on the most appropriate definition. According to the 2001 National Cholesterol Education Program (NCEP) criteria, the metabolic syndrome is defined by the presence of three or more of the following risk factors: (i) abdominal obesity (i.e. waist circumference of greater than 102 centimeters for men and of greater than 88 centimeters for women); (ii) triglyceride levels equal to or greater than 150 mg/dL; (iii) HDL cholesterol of lower than 40 mg/dL for men and of lower than 50 mg/dL for women; (iv) a systolic blood pressure of equal to or greater than 130 mmHg and/or a diastolic blood pressure equal to or greater than 85 mmHg; and (v) fasting glucose levels equal to or greater than 110 mg/dL. The more recent American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement³ has slightly modified these criteria by reducing the cut-off for elevated fasting glucose to equal to or greater than 100 mg/dL. Finally, the International Diabetes Federation has provided an alternative definition of the syndrome by requiring the mandatory presence of central obesity plus any two of the remaining criteria.⁴ Regardless of the definition, the metabolic syndrome is a serious public health problem. In the United States it affects approximately 25% of adults over the age of 20 and up to 45% of the population over 50 years old, although its prevalence varies substantially by ethnicity.⁵

Recent studies from Europe reported that the prevalence of the metabolic syndrome ranges between 5 and 20% in the adult population, according to the different definitions used.^{6–8} Affected patients have a significantly increased risk of developing diabetes, coronary artery disease and ischemic stroke.^{6,9–13} In a prospective population-based study, Lakka and co-workers assessed the association between the metabolic syndrome

and cardiovascular and overall mortality in 1200 Finnish men free of symptomatic cardiovascular disease or diabetes at baseline.⁶ After a mean follow-up of 11 years, both cardiovascular and all-cause mortality were increased in men with the metabolic syndrome. Similar results were found in a larger population-based study performed by McNeill *et al.*,⁹ in which the incidence of cardiovascular disease in more than 12000 multiracial individuals was analyzed. After a mean follow-up of 11 years, 879 coronary events and 216 ischemic stroke events occurred, and the presence of the metabolic syndrome was associated with an increased risk of developing cardiovascular outcomes. These results were further confirmed when specific populations or specific outcomes were considered. For example, in the *Progetto Ipertensione Umbria Monitoraggio Ambulatoriale* (PIUMA) study,¹⁰ the incidence of cardiovascular events in a population of 1742 hypertensive patients without symptomatic cardiovascular disease was prospectively assessed. In this population, the presence of the metabolic syndrome amplified cardiovascular risk associated with high blood pressure independently of the effect of other traditional cardiovascular risk factors.

In recent studies, the metabolic syndrome was also identified as an independent risk factor for stroke. In a case-control study, Milionis and colleagues compared the prevalence of the metabolic syndrome in a group of 163 patients older than 70 years with a first episode of ischemic non-cardioembolic stroke and in 166 controls.¹¹ In this study, the metabolic syndrome resulted significantly more prevalent in patients with acute ischemic stroke (46.0%) than in controls (15.7%) and this association remained significant after adjustment for other potential risk factors for stroke (OR 5.33; 95% CI: 2.91, 9.79). Two prospective cohort studies carried out in patients with coronary heart disease and in patients with no history of cardiovascular disease confirmed these findings.^{12,13} In one study, more than 14000 patients with coronary heart disease were followed for over 4.8 to 8.1 years: patients with the metabolic syndrome without diabetes had a 1.49-fold increased risk of transient ischemic attack or stroke (95% CI: 1.20–1.84) in comparison to patients without the metabolic syndrome.¹² In the other study, carried out in 1131 men, after a mean follow-up of 14.3 years, patients with the metabolic syndrome had a 2.05-fold increased risk for all strokes (95% CI: 1.02–4.11) in comparison to patients without the metabolic syndrome.¹³

The increased risk of cardiovascular disease in patients with the metabolic syndrome is probably associated with the inflammatory and hypercoagulable states that may occur in these patients. In the presence of visceral obesity, several circulating inflammatory adipokines, including tumor necrosis factor α (TNF α), leptin, interleukin-6 (IL-6) and angiotensinogen, are produced by the adipose tissue,¹⁴ thus underlying the pivotal role of visceral obesity in this syndrome. TNF α inhibits insulin signaling thus contributing to insulin resistance. Leptin activates the immune system and increases blood pressure. IL-6 stimulates the hepatic production of C-reactive protein in obese subjects.¹⁵ Angiotensin II (produced from angiotensinogen) exerts its adverse endocrine effects via the angiotensin II type 1 receptor (AT1), leading to oxidative stress, vasoconstriction, aldosterone secretion, renal sodium resorption, sympathetic stimulation, vasopressin release, plasminogen activator inhibitor-1 (PAI-1) expression and, possibly, to thrombosis.¹⁶

In contrast to these adipokines, adiponectin, a circulating collagen-like molecule also produced by adipose tissue, is inversely correlated with the fat mass in obese subjects. Adiponectin enhances insulin sensitivity and inhibits inflammatory effects on the endothelium, largely through inhibiting TNF α activation of nuclear factor κ B.¹⁷ Furthermore, adiponectin stimulates the production of nitric oxide in endothelial cells,¹⁸ and serum levels of C-reactive protein are reciprocally associated with adiponectin levels, thus suggesting a potential link between adiponectin and coronary artery disease.¹⁹

The metabolic syndrome is also associated with increased plasma levels of fibrinogen, factor VII and factor VIII, thus leading to a potential hypercoagulable state, and with

increased levels of PAI-1, thus leading to a hypofibrinolytic state. Increased levels of fibrinogen are associated with both chronic inflammation and insulin resistance in the metabolic syndrome.²⁰ Low-grade chronic inflammation has been associated with increased release of soluble tissue factor and factor VII.^{21,22} Furthermore, factor VII activity correlates with both body mass index and triglyceride levels.²³ The simultaneous increase in both soluble tissue factor and factor VII clearly enhances the risk of activation of the coagulation cascade. Increased levels PAI-1 are common in subjects with the metabolic syndrome. Insulin resistance and chronic inflammation contribute to the increase in PAI-1.^{24–26} Finally, decreased plasma tissue plasminogen activator activity is related to insulin resistance in patients with characteristics of the metabolic syndrome.²⁷

Overall, these changes contribute to attenuation of plasminogen conversion, resulting in a hypofibrinolytic state. Finally, endothelial dysfunction (measured by flow-mediated dilation to assess nitric oxide bioavailability) is commonly found in patients with the metabolic syndrome, and is directly correlated with increased cardiovascular risk.²⁸ The induction of endothelial dysfunction has been associated with the presence of hyperinsulinemia and dyslipidemia. Platelets from obese insulin-resistant subjects have reduced sensitivity to the anti-aggregatory effects of insulin.²⁹ Moreover, very-low-density lipoprotein and triglycerides have been shown to increase platelet aggregability, whereas this effect is reversed by HDL cholesterol.^{30–32}

Given the solid evidence of an inflammatory and a hypercoagulable state in these patients, there is a rationale to hypothesize that the metabolic syndrome may also predispose patients to develop venous thromboembolic events. Recent studies have investigated this association.

In a case-control study we compared the prevalence of the metabolic syndrome diagnosed according to the 2001 NCEP criteria in a group of 93 patients with a first episode of unprovoked deep vein thrombosis (DVT) and in 107 controls.³³ In this study, the metabolic syndrome was significantly more prevalent in patients with unprovoked DVT (50.5%) than in controls (34.6%) and this association remained significant after adjustment for age, sex, body mass index, and smoking (OR 2.16; 95% CI 1.19, 3.90). In this issue of the journal, Ay and colleagues present the results of a case-control study on the prevalence of the metabolic syndrome in 116 patients with objectively confirmed recurrent venous thromboembolism, who had had at least one unprovoked event, and 129 age and sex-matched healthy controls.³⁴

Once again, the prevalence of the metabolic syndrome was significantly higher in patients (40/116, 35%) than in controls (26/129, 20%) with a resulting unadjusted OR of 2.1 (95% CI 1.2, 3.7). This association remained statistically significant after adjustment for other established risk factors for thrombosis, sex and age (OR 2.2, 95% CI 1.1, 4.3). Although the prevalence of the metabolic syndrome in patients and in controls was different in these two studies (in part because of the differences in the mean age of the two populations), the magnitude of the association between the metabolic syndrome and venous thromboembolic disease was similar. Therefore, taken together, the results of the two studies corroborate the hypothesis that the metabolic syndrome may also play a role in the pathogenesis of venous thromboembolic disease.

This hypothesis is particularly relevant in the light of recent clinical observations which challenged the common concept that venous thromboembolism and atherosclerosis are two distinct entities.^{35–37} However, larger prospective studies are now needed to confirm these preliminary results.

In conclusion, the metabolic syndrome has been shown to be an important cluster of cardiovascular risk factors placing patients at an increased risk of coronary artery disease and ischemic stroke. Because these patients have both an inflammatory state and a hypercoagulable state, the metabolic syndrome may also predispose to venous

thromboembolism. Thus, diagnosing and adequately managing the metabolic syndrome is an important step in the process of preventing cardiovascular disease. Even if some authors have raised the question of whether the syndrome is really more than the sum of its components,³⁸ it remains a relevant target for clinical practice. Indeed, the benefits of adequate management have been shown also in patients having only some features of the syndrome.³⁹

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