Metabolic syndrome and hyperhomocysteinemia in patients with deep vein thrombosis: a case-control study

We evaluated the prevalence of the metabolic syndrome (MS) and of hyperhomocysteinemia in patients with unprovoked deep vein thrombosis (DVT) and in controls. The MS and hyperhomocysteinemia were significantly more prevalent in DVT patients than in controls. However, only the MS resulted independently associated with DVT, and the coexistence of both risk factors did not increase the magnitude of the association.

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High plasma homocysteine levels are common in patients who have suffered venous thromboembolic event (VTE), and several case-control studies and recent meta-analyses have shown higher plasma homocysteine levels in patients with VTE compared to controls.[1]

The metabolic syndrome (MS), a group of cardiovascular risk factors, is associated with a 3 to 4 fold increase in the incidence of cardiovascular disease.[2,3] Hyperhomocysteinemia seems to be an additional risk factor for cardiovascular disease in patients affected by the MS.[4,5] We recently found that patients with unprovoked deep vein thrombosis (DVT) had a significantly higher prevalence of the MS than control subjects without thrombosis suggesting the MS has a role in the pathogenesis of DVT.[6] However, there have been no studies to assess the relationship between hyperhomocysteinemia and the MS in the pathogenesis of DVT.

This study evaluates part of the population included in our previous study[6] to determine whether the presence of the MS is associated with elevated levels of homocysteine in patients with DVT, and to assess the relationship between the MS and plasma homocysteine levels in these patients. In a case-control study, consecutive patients with objectively confirmed, unprovoked DVT and control subjects with objectively excluded DVT underwent clinical assessment for the presence of the MS according to the National Cholesterol Education Program criteria.[7] Fasting plasma levels of total homocysteine were measured in patients and in controls. Hyperhomocysteinemia was defined by homocysteine levels above 15 μmol/L. Odds ratios (ORs) and 95% confidence intervals (CIs) were used as a measure of association between DVT and hyperhomocysteinemia and between DVT and the presence of the MS. Interaction between hyperhomocysteinemia and the MS on the development of DVT was evaluated using a logistic regression model. Eighty four patients with unprovoked DVT and 94 controls were enrolled.

Patients' baseline characteristics are summarized in Table 1. Hyperhomocysteinemia was significantly more common in patients with unprovoked DVT than in controls (32/84 vs 27/94; OR 1.95; 95% CI 1.00-3.81). There was no significant difference in mean homocysteine levels between patients with unprovoked DVT and in controls (18.7 vs 15.0 μM; p=0.08). Adjustment for possible confounding factors (age, gender, smoking habits) did not affect results.

Hyperhomocysteinemia was significantly more common in patients with the MS than in patients without (35/75 vs 29/103; OR 2.23; 95% CI 1.14-4.28). After multivariate analysis, the presence of hyperhomocysteinemia remained independently associated with the presence of the MS.

Table 1. Baseline characteristics.

	Idiopathic DVT	*Controls*	*p*
Number	84	94	
Caucasian n (%	84 (100)	94 (100)	NS
Mean age, years (SD)	64.7 (14.7)	63.9 (14.5)	NS
Male sex n (%)	53 (63.1)	38 (39.2)	0.003
BMI >29.9 Kg/m^2 n (%)	27 (32.1)	19 (20.2)	0.07
Smoking habit n (%)	14 (16.7)	21 (22.3)	NS
History of symptomatic atherosclerosis n (%)	11 (13.1)	12 (12.0)	NS

DVT deep vein thrombosis, BMI body mass index, SD standard deviation. Results of Student's t test are expressed as p values Results of χ^2 test are expressed as odds ratios (plus or minus 95% confidence intervals).

Twenty two patients with unprovoked DVT (26.2%) and 12 controls (12.8%) had both hyperhomocysteinemia and the MS. This association was significantly more prevalent in patients with unprovoked DVT than in controls (OR 2.42; 95% CI 1.05-5.67).

The MS was significantly more common in patients with idiopathic DVT than in controls (43/84 vs 32/94; OR 2.03; 95% CI 1.06-3.89). Multivariate analysis was performed to assess factors associated with unprovoked DVT and controls. This analysis found male gender (OR 2.64; 95% CI 1.40, 4.98) and the MS (OR 2.14; 95% CI 1.12, 4.08) to be independently associated with unprovoked DVT, whereas the presence of hyperhomocysteinemia was not seen to be independently associated with the presence of unprovoked DVT.

In conclusion, we found that hyperhomocysteinemia was significantly more common in patients with the MS than in patients without. This association remained significant after controlling for potential confounders. Although both the MS and hayperhomocysteinemia were significantly more prevalent in DVT patients than in controls, only the MS resulted to be independently associated with DVT, and the coexistence of both risk factors did not increase the magnitude of the association.

A number of studies and meta-analyses[1,8,9] have reported an association between hyperhomocysteinemia and DVT. The mechanisms by which hyperhomocysteinemia might induce DVT have not been completely clarified, but may include effects on the endothelium and on the coagulation cascade.[10] Given the high prevalence of hyperhomocysteinemia in patients with the MS, and the recently reported association between this latter and unprovoked DVT, there was a rationale to suggest that hyperhomocysteinemia might have been the cause of such association. However, the results of our study suggest that the potential role of the MS in the pathogenesis of unprovoked DVT is not mediated by the presence of hyperhomocysteinemia. On the contrary, when adjusted for the presence of the MS, hyperhomocysteinemia was not seen to be an independent risk factor for DVT, and its increased prevalence in patients with unprovoked DVT

may be explained, at least in part, by the presence of the MS. Therefore, it is possible that hyperhomocysteinemia is an epiphenomenon rather than a risk factor. However, these preliminary results need to be confirmed in larger prospective studies.

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Key words: metabolic syndrome, hyperhomocysteinemia, deep vein thrombosis.

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