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Letter to the Editor

Divergent associations of tissue inhibitors of metalloproteinases-1 and -2 with the prothrombotic/fibrinolytic state☆

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Dear Editor,

Tissue inhibitors of metalloproteinases (TIMPs) selectively block the active site of matrix metalloproteinases (MMPs), and they are thus involved in the turnover of the extracellular matrix [1,2]. Although there is evidence suggesting that high circulating TIMP-1 level is associated with cardiac function [3–5], atherosclerosis [6], and cardiovascular risk [7,8], studies regarding the clinical associations of circulating TIMP-2 level are limited [9,10]. Interestingly, recent evidence indicates a mechanistic cross-talk between proteins involved in the haemostasis/fibrinolysis, which are implicated in the pathophysiology of atherothrombotic cardiovascular disease [11,12], and proteins regulating the metabolism of the extracellular matrix. For example, plasmin, a major regulator of fibrinolysis, is also an activator of several MMPs [1]. Furthermore, the activity of the urokinase-type plasminogen activator, which is a central mediator of pericellular proteolysis, is inhibited by plasminogen activator-inhibitor-1 (PAI-1) [1]. However, data regarding the relationship of TIMPs with the prothrombotic/fibrinolytic state are lacking so far. Accordingly, in the present cross-sectional study we sought to investigate the possible association between circulating TIMP-1 and TIMP-2 and the prothrombotic/fibrinolytic balance assessed by levels of fibrinogen and PAI-1, in apparently healthy individuals.

As part of a broader research of our Department investigating atherosclerotic risk factors and vascular function [13,14], we measured circulating levels of TIMPs, fibrinogen, PAI-1 and high-sensitivity C-reactive protein (hsCRP) in 212 apparently healthy adults (age 41.4 ± 8.2 years [mean ± S.D.], 140 males and 72 females) who were randomly selected from the employees' records of two large industries. All subjects were studied in the morning after an overnight fast and underwent a detailed clinical interview and examination. Participants who had evidence of hypertension, diabetes mellitus, cardiovascular disease, a family history of premature vascular disease, any kind of acute inflammatory-infectious or chronic disease were excluded from the study. Subjects who were taking regular medications or took any medication during the last week were also excluded. TIMPs and PAI-1 were measured with ELISA (Quantikine, R&D Systems, Minneapolis, MN, USA and Asserachrom, Diagnostica Stago, Asnieres, France, respectively). Fibrinogen and high-sensitivity CRP (hsCRP) was measured by immunonephelometry (Dade Behring, Marburg, Germany). Skewed variables (TIMP-2, PAI-1 and hsCRP) were log-transformed prior to any parametric analysis.

Overall, values for TIMP-1, TIMP-2, fibrinogen, PAI-1 and hsCRP were 218.0 ± 81.3 ng/mL, 114.2 (89.2–150.7) ng/mL (median [interquartile range]), 225.2 ± 74.6 mg/dL, 9.04 (5.91–15.35) ng/mL, and 0.97 (0.52–2.19) mg/L, respectively. We observed a significant correlation of hsCRP with TIMP-1 ($r = 0.15$, $P < 0.05$), but not with TIMP-2 ($r = -0.036$, P = NS). In univariate analysis, we observed a significant correlation of TIMP-1 level with fibrinogen ($r = 0.265$, $P < 0.001$) and a borderline correlation with PAI-1 ($r = 0.133$, $P = 0.053$) (Fig. 1). On the other hand, TIMP-2 level was inversely associated with both fibrinogen ($r = -0.209$, $P < 0.01$) and PAI-1 ($r = -0.134$, $P = 0.05$) (Fig. 1).

In addition, we performed multivariable linear regression analysis to investigate whether TIMPs are independently associated with prothrombotic markers, after adjusting for potential confounders (factors that determine the prothrombotic/fibrinolytic balance), such as age, gender, systolic blood pressure, smoking status, body mass index, blood glucose, lipid profile (total cholesterol and triglycerides) and subclin-

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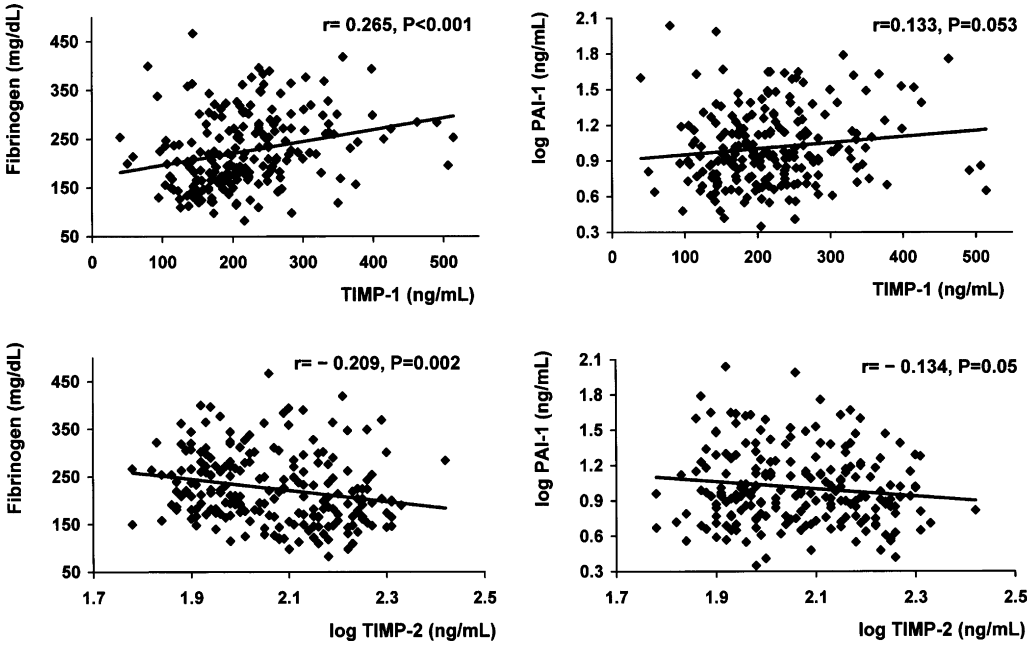

Fig. 1. Correlations (Pearson's coefficients) between haemostatic/fibrinolytic markers (fibrinogen and PAI-1) and TIMPs (TIMP-1 and TIMP-2) in the study population.

ical inflammation (hsCRP). In such models, TIMP-1 was an independent determinant of fibrinogen level (Model 1, Table 1) but not of PAI-1 level (data not shown). On the other hand, we observed significant negative associations of TIMP-2 with both fibrinogen and PAI-1, independent of clinical characteristics and risk factors (Models 2 and 3, Table 1).

The present study shows for the first time that, in apparently healthy individuals, circulating TIMP-1 level has an independent positive correlation with plasma fibrinogen concentration. In contrast, a high TIMP-2 level is associated with a favourable prothrombotic/fibrinolytic balance as evaluated by low concentrations of fibrinogen and PAI-1. Our study provides the first observational evidence for a differential relationship of TIMP-1 and TIMP-2 with haemostatic proteins. These findings highlight the role of TIMPs as markers of the prothrombotic state and imply that they perhaps have divergent roles in the haemostasis and the thrombogenicity of apparently healthy adults.

Recent studies in subjects free of cardiovascular disease have shown that circulating TIMP-1 is associated with Framingham risk score [3], subclinical atherosclerosis [6], and left ventricular systolic [3] and diastolic dysfunction [4,5]. Moreover, TIMP-1 level is an independent predictor of adverse outcomes in patients with established or suspected coronary artery disease [7,8]. Given that haemostatic factors are related to incident atherosclerotic disease [11] and cardiovascular outcomes [12], our study suggests that the

Table 1
Multiple regression models evaluating the association of fibrinogen with TIMP-1 (Model 1) and TIMP-2 (Model 2), and the association of PAI-1 with TIMP-2 (Model 3)

	Unstandardized coefficient	Standardized coefficient	*P*-Value
Model 1 (dependent variable: fibrinogen)			
Age (years)	1.170	0.128	0.054
TIMP-1 (ng/mL)	0.245	0.267	<0.001
Model 2 (dependent variable: fibrinogen)			
Age (years)	1.471	0.161	0.018
Log TIMP-2 (ng/mL)	−129.145	−0.234	0.001
Model 3 (dependent variable: log[PAI-1])			
Systolic BP (mmHg)	0.004	0.175	0.010
BMI (kg/m^2)	0.014	0.160	0.020
Log triglycerides (mg/dL)	0.484	0.315	<0.001
Log TIMP-2 (ng/mL)	−0.291	−0.124	0.042

BMI, body mass index; BP, blood pressure; TIMP, tissue inhibitor of metalloproteinases.