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The complex between tPA and PAI-1: risk factor for myocardial infarction as studied in the SHEEP project

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Abstract

Introduction: The tPA/PAI-1 complex seems to be an important biochemical marker for myocardial reinfarction. Therefore we explored the distribution, correlation and interaction of plasma concentrations of tPA/PAI-1 complex in all available patients and matched controls in the Stockholm Heart Epidemiology Program (SHEEP).
Methods and patients: The SHEEP study is a case control study of 2246 patients with a first myocardial infarction (MI), of which 1267 surviving patients were subjected to blood sampling about 3 months after MI and compared with a control group, matched for age, sex and living area within the Stockholm County. The study consists of 886 (591 men and 295 women) patients and 1198 (753 men and 445 women) matched controls, who were all analysed for plasma tPA/PAI-1 complex.
Results: The plasma concentration of tPA/PAI-1 complex was significantly associated with the risk for MI, for both genders. Synergistic interactions were observed in men

Abbreviations: SHEEP, Stockholm Heart Epidemiology Program; S, Synergy index scores; CI, confidence intervals; OR, odds ratios.

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for the co exposure to high plasma tPA/PAI-1 complex concentrations in combination with smoking (OR=4.6) or diabetes mellitus (OR=7.9). Synergism was also seen in combination with exposure to serum hypercholesterolemia or increased levels of apolipoprotein B. An antagonistic effect of the co exposure to high tPA/PAI-1 complex and hypertension was found among men with a similar tendency among women, but an antagonistic effect of increased waist/hip ratio was only observed among the women.
Conclusions: Measuring the plasma concentration of tPA/PAI-1 complex might be of practical value in assessing risk of MI for both genders, especially in those who are smokers or in patients with manifest diabetes mellitus.

Introduction

An impaired fibrinolytic function, mainly due to increased plasma PAI-1 levels, is strongly correlated to the development of MI. This has been clearly demonstrated in several prospective [1—6] and retrospective [7,8] studies. It has also been found that tPA antigen [9,10] or tPA/PAI-1 complex [11] in plasma might be an even better predictor of MI. The reason for this is not well understood, but tPA/PAI-1 complex in plasma, which constitutes the most important part of tPA antigen, correlates very well to the plasma PAI-1 activity concentrations [12]. On the other hand, it does not correlate at all with tPA activity, which constitutes only a few % of the total tPA in plasma. The active PAI-1 molecule is not stable at physiological conditions, but is slowly transformed into a latent inactive form. Also, it is subjected to quite an extensive diurnal variation, with the highest levels in the very early morning. At the time when blood samples are normally taken in patients, between 8 and 10 am, the concentration of PAI-1 is rapidly declining. The complex between tPA and PAI-1 is also subjected to a diurnal variation, but much less as compared to PAI-1. Therefore it seems that the complex between tPA and PAI-1 is a more reliable way to get a true estimate of the PAI-1 levels in plasma. Recently we were able to demonstrate that tPA/PAI-1 complex is a quite strong predictor of reinfarction among the patients in the Stockholm Heart Epidemiology Program (SHEEP) study that already had a first cardiovascular event prior to inclusion in the study [11]. The SHEEP study consists of virtually all patients (45—70 years old) of Swedish origin in the Stockholm County with a first MI between 1992 and 1993 (men) or 1992 and 1994 (women). 1267 of these patients, who survived until at least 3 months after the first event, was subjected to blood sampling and compared with a control group, matched for age, sex and living area within the Stockholm County [13].

In the present study we decided to explore more closely the distribution of plasma concentrations of tPA/PAI-1 complex in all patients and controls included in the SHEEP study. This provides data regarding a primary infarction, which has not been published previously. This is important, especially since the mechanism for reinfarction and a primary infarction might be different. In addition, we also investigated its distribution in subpopulations of the SHEEP material and evaluated correlations and possible interactions. Since the tPA/PAI-1 complex seems to be one of the most important biochemical markers for MI, it was considered important to put it into perspective of other factors of importance for the development of this disease.

Materials and methods

Patients and controls

The Stockholm Heart Epidemiology Program (SHEEP) is a case-control study in which 2246 patients (1485 men and 761 women) with a first MI were identified. From the survivors 1267 (893 men and 374 women) were subjected to blood sampling about 3 months after the primary event. They were compared with 1563 (1054 men and 509 women) control subjects matched for age, sex and hospital catchments area. All individuals were subjected to a health control at the same time as the blood sampling was carried out. A specific analysis of tPA/PAI-1 complex was performed in 886 of the patients (591 men and 295 women) and in 1198 (753 men and 445 women) of the matched control subjects. These constituted the study group in the present investigation. The patients and controls (age 45—70 years) were all