The plasminogen activator inhibitor-1 4G/5G and tissue plasminogen activator Ala-repeat insertion/deletion polymorphisms might be genetic determinations of increased or decreased of their plasma activities. The aim of this study was to investigate the association of plasminogen activator inhibitor-1 4G/5G and tissue plasminogen activator Ala-repeat I/D polymorphisms with metabolic syndrome parameters in normal Malaysian subjects and to assess the impact of these polymorphisms on their plasma activities and antigens. The genetic polymorphisms were genotyped in 130 normal subjects. In addition, the plasma activities and antigens of plasminogen activator inhibitor-1 and tissue plasminogen activator as well as levels of insulin, glucose, and lipid profile at fasting state were investigated. The subjects with homozygous 4G/4G showed association with an increased triglyceride (p = 0.007), body mass index (p = 0.01) and diastolic blood pressure (p = 0.03). In addition, the plasminogen activator inhibitor-1 4G/5G polymorphism modulates plasma plasminogen activator inhibitor-1 activity and antigen and tissue plasminogen activator activity (p = 0.002, 0.014, 0.003) respectively. These results showed that, the plasminogen activator inhibitor-1 4G/5G polymorphism is associated with metabolic syndrome parameters, plasminogen activator inhibitor-1 and tissue plasminogen activator activities in Malaysian subjects, and may serve to increase the risk of type 2 diabetes and cardiovascular disease in Malaysian subjects.

Key Words: plasminogen activator inhibitor-1, tissue plasminogen activator, type 2 diabetes, metabolic syndrome, cardiovascular disease

Plasminogen activator inhibitor-1 4G/5G polymorphism is associated with metabolic syndrome parameters in Malaysian subjects


1Department of Molecular Medicine, Faculty of Medicine and 2Department of Medicine, University of Malaya Medical Centre, University of Malaya, 50603 Kuala Lumpur, Malaysia
2Department of Biochemistry, Faculty of Medicine, Sana'a, Yemen
3Faculty of Dentistry, Ibb University, Yemen

(Received 13 April, 2011; Accepted 24 June, 2011)

The collected blood immediately taken into five labelled Vacutainer tubes, 0.109 M EDTA, were subjected to the APAP test on the same day. The plasma was separated from the blood by centrifugation at 3000 rpm for 10 minutes and was stored at -80°C. The procedures for the APAP test were as described in our earlier studies.30 The constellation of these metabolic abnormalities known as a metabolic syndrome (MetS) or insulin resistance syndrome increases the risk of T2D and CVD. The number of individuals with the MetS has increased globally during the past two decades, and this increase is associated with the worldwide epidemic of obesity and diabetes.31 High PAI-1 levels have been reported in obese and MetS subjects.32,33 Increase in plasma proinsulin, C-peptide and insulin, have also been associated with high levels of PAI-1.34

Plasma PAI-1 is the major physiological inhibitor of endogenous fibrinolysis. It inhibits the action of tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), often leading to fibrin accumulation in basement membranes and interstitial tissues.35-38 Elevation in plasma PAI-1 appears to compromise normal fibrin clearance mechanisms and promotes thrombosis.

Several SNPs in the PAI-1 gene have been identified,39 among which the 4G/5G polymorphism (rs1799889) located in the promoter region –675 bp upstream from the mRNA synthesis initiation point has been quite extensively studied. Association of this polymorphism and variables related to the MetS were, however, unclear which carriers of the 4G allele being more prone to obesity and MetS in some studies,39 but not in others.40-42

Alu repeat I/D polymorphism was found in intron 8 of the tPA gene.43 This Alu repeats probably arose early in human evolution, and a number of populations have been found to be dimorphic for its presence or absence of repeats.44 This polymorphism, however, not significantly correlated with basal endothelial tPA synthesis.45

The PAI-1 4G/5G and tPA polymorphisms and their role in modulating plasma levels of PAI-1 and tPA activities and antigens have not been reported in Malaysian subjects. We studied the association of PAI-1 4G/5G and tPA polymorphisms with MetS parameters and plasma levels of PAI-1 and tPA activities and antigens in normal Malaysian subjects.

Materials and Methods

Subjects and data collection. In this study, normal subjects without diabetes and MetS in the Klang Valley, Kuala Lumpur were recruited. The study was approved by the Medical Ethics Committee of University Malaya Medical Centre. Written informed consent was obtained from each subject. Blood pressure (BP) measurements were taken from each subject's right arm in the seated position by using an Omron Intellisense Automatic Blood Pressure Monitor after 10 min of rest in a quiet room in the morning. Between two and three successive BP readings were obtained at 5-min intervals and averaged. Body weight and height were measured and BMI was computed as weight (kg) divided by height (m²). Waist circumference was measured midway between the lower rib margin and the superior iliac spine at the end of gentle expiration in a standing position.

Fasting venous blood (10 ml) was collected from each subject within a 2 h window (8:00 to 10:00 AM) after 15 min rest, because of the diurnal variation of plasma PAI-1.46 The collected blood immediately taken into five labelled Vacutainer tubes, 0.109 M EDTA.