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Original Article

Physiology Section

# Plasminogen Activator Inhibitor-1 as a Marker of Thrombosis among Prehypertensive Patients: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Impaired endogenous fibrinolysis has been shown to play a role in the pathogenesis and complications of hypertension. Plasminogen Activator Inhibitor-1 (PAI-1) is said to be a predictor of impaired fibrinolysis and thrombosis. Prehypertension is a common worldwide condition and is known to be an independent risk factor for Cardiovascular Disease (CVD).

**Aim:** Present study aimed to measure plasma PAI-1 levels in prehypertensive patients and normal subjects and to find the correlation between elevated PAI-1 levels with Blood Pressure (BP), triglycerides, total cholesterol, Low-Density Lipoproteins (LDL) cholesterol, High-Density Lipoproteins (HDL) cholesterol, and urine albumin.

**Materials and Methods:** This cross-sectional analytical study included 100 patients, comprising 50 prehypertensive individuals and 50 controls, aged between 35 and 50 years. The study was conducted at Sapthagiri Institute of Medical Sciences and Research Centre in Bangalore, India. Anthropometric measurements, PAI-1 levels, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and urine albumin were measured using standard procedures. The data were statistically analysed using the Statistical Package for Social Sciences (SPSS) version 10.0, applying Student t-test and Chi-square test. Correlation analysis was performed to assess the relationship between PAI-1 and various parameters.

**Results:** A total of 100 patients were included in the study which had 64 men and 36 women with a mean age of 46±7 years. PAI-1 levels were significantly higher in the prehypertensive group compared to the control group (p-value=0.013). Participants with higher plasma PAI-1 levels had significantly elevated BP (p-value=0.001) compared to those with lower PAI-1 levels. Total cholesterol, triglycerides, and LDL cholesterol were significantly increased in prehypertensive individuals (p-value=0.001), whereas HDL cholesterol was significantly lower (p-value=0.001). The study also observed a significant increase in urine albumin in the prehypertensive group with elevated PAI-1 levels compared to the controls (p-value=0.001).

The study revealed that elevated plasma PAI-1 levels did not show a significant positive correlation with SBP and DBP (r=0.138 and 0.660, p-value of 0.338 and 0.648, respectively). Plasma PAI-1 levels were weakly correlated with total cholesterol (r=0.145, p-value 0.315), LDL cholesterol (r=-0.068, p-value 0.640), HDL cholesterol (r=0.21, p-value 0.882), and triglycerides (r=0.207, p-value 0.150). There was no significant correlation between increased PAI-1 levels and urine albumin (r=-0.225, p-value of 0.117).

**Conclusion:** Present study demonstrated that plasma PAI-1, total cholesterol, triglycerides, LDL cholesterol, and urine albumin were significantly elevated in prehypertensive individuals, suggesting vascular damage and inflammation. As prehypertension is often asymptomatic, patients with prehypertension should be considered to have an increased risk for CVD.


**Keywords:** Cardiovascular disease, Fibrinolysis, Inflammation

## INTRODUCTION

Hypertension is an important worldwide public health problem. It is a known predictor of CVD, cerebrovascular accidents, chronic renal failure, and end-stage kidney disease. Globally, more than 17 million premature deaths are attributed directly or indirectly to hypertension and its complications [1]. Hypertension is the fourth highest risk factor responsible for the greatest number of deaths and disabilities, with nearly 11% of all deaths attributable to hypertension in India [2,3]. Prehypertension is also associated with an increased risk of cardiovascular complications. The Joint National Committee (JNC7) on prevention, detection, evaluation, and treatment of high blood pressure defined prehypertension as SBP of 120 to 139 mmHg or DBP of 80 to 89 mmHg, based on two or more properly measured seated blood pressure readings on each of two or more office visits [4]. Previous studies conducted on the Indian urban population have reported a prevalence of prehypertension close to 32%, which was closely associated with age groups, gender, occupation, and high Body Mass Index (BMI) [5-7].

Epidemiological studies have shown that the risk of prehypertension progressing to hypertension and developing CVD is higher in individuals with blood pressure of 130 to 139/85 to 89 mmHg than in those with blood pressure of 120 to 129/80 to 84 mmHg [8-11].

The pathophysiology of hypertension is associated with impaired endogenous fibrinolytic activity, accelerated atherosclerosis, and clot formation, which play a major role in the complications of hypertension. Recent studies have demonstrated great concern about prehypertension, as it is an independent risk factor for CVD, increasing the risk of thrombosis and altered hemostasis [12-14].

Plasminogen Activator Inhibitor-1 (PAI-1), a member of the serine protease inhibitor family, is the major regulator of the endogenous fibrinolytic system. PAI-1 is the primary physiological inhibitor of plasminogen activation in the blood. It acts by inhibiting tissue-type (tPA) and urokinase-type plasminogen (uPA) activators [15]. PAI-1 is largely secreted by vascular endothelial cells, platelet alpha granules, hepatocytes, adipocytes, and cardiomyocytes. In pathological conditions, PAI-1 secretion is increased by proinflammatory factors such as TNFα, TGFβ, IL6, lipoproteins, growth factors, and insulin in response to inflammation [16]. Juhan-Vague et al., reported in their study on PAI-1 in cardiovascular pathology that increased plasma PAI-1 is predictive of myocardial infarction. It creates a prothrombotic state that contributes to the development of CVD. Studies also

suggest that inflammation has a role in inducing the secretion of plasma fibrinolytic markers in hypertension [15-19]. PAI-1 secretion is closely associated with the Renin-Angiotensin System (RAS), an important contributor to vascular disease initiation and progression. Treatments that inhibit the Renin Angiotensin-Aldosterone System (RAAS) also decrease PAI-1 [20].

Abnormal levels of serum lipids constitute one of the important independent risk factors for CVD and studies estimate that they account for 56% of Coronary Heart Disease (CHD). Studies have shown PAI-1 overexpression in glomerulosclerosis through interstitial macrophage recruitment and activation [1,21]. Prehypertension, most often asymptomatic and goes unrecognised, has not been widely studied regarding impaired fibrinolysis, especially in the Indian population [22].

The present study aims to measure plasma PAI-1 in prehypertensive patients and normal subjects, and to find the correlation between elevated PAI-1 levels with blood pressure, triglycerides, total cholesterol, LDL, HDL cholesterol, and urine albumin in prehypertensives.

## MATERIALS AND METHODS

The present study is a cross-sectional analytical study conducted on patients attending the Outpatient Department (OPD) of General Medicine at Sapthagiri Institute of Medical Sciences and Research Centre in Bangalore, India, over a period of one year from October 2020 to September 2021. The study protocol was approved by the ethical committee of the institute, ensuring the confidentiality of the data (SIMS and RC/IECC/05/2018). A total of 100 participants, including 50 prehypertensive patients and 50 controls, were included in the study in the age group of 35 to 50 years. Prehypertension was defined according to the JNC-7 classification [4]. The sample size was calculated based on a prevalence of prehypertension of 32%, as determined by a previous study conducted in South India [5,6].

$$n=\frac{4pq}{d^2}$$ (p=prevalence (32%), q=100-p=68, d=20%)

**Inclusion criteria:** A total of 50 prehypertensive individuals in the age group of 35-50 years and 50 controls between 35-50 years, including both male and female patients, were included.

**Exclusion criteria:** Patients with the following comorbidities, such as Type 2 diabetes mellitus, individuals taking antihypertensive medication, sepsis, obesity, history of thrombosis, cardiovascular diseases, and renal diseases, were excluded from the study.

Blood Pressure (BP) was measured three times by trained staff using a standard mercury sphygmomanometer (Diamond) following a standardised protocol, after the participants had rested for at least five minutes, during two separate visits. The mean of the last two measurements was used for statistical analysis.

Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters (kg/m$^2$). Waist and hip circumference were measured using a flexible plastic tape at the level of the abdomen (midway between the lower rib margin and the iliac crest) and the hip (over the greater trochanters).

Plasma PAI-1 was analysed using an Enzyme-Linked Immunosorbent Assay (ELISA) with a commercially available kit (KINESISDx Catalogue No K12-1160) from Skanda Life sciences, Bangalore. The kit is DSIR recognised and CPCSEA approved, and the Human PAI-1 ELISA Report No is: SLSPL/2021/AN/11/023/01. Venous blood samples were collected with minimal venous occlusion to prevent activation of haemostatic factors. The samples were collected between 8 am to 10 am to minimise the effects of diurnal variations on PAI-1. Blood samples were centrifuged gently for 10 minutes, and platelet-poor plasma was collected and stored at -70ºC.

Total cholesterol, triglycerides, HDL, and LDL cholesterol measurements were performed using the enzymatic method (Vitros 5600 catalogue J56001504) [23,24]. Plasma glucose was measured using the glucose oxidase peroxidase method (Vitros 5600 catalogue J56001504) [25], to rule out diabetes mellitus. Urine albumin was measured using the standard laboratory turbidimetry method (Vitros chemistry Products mALB Reagent) [26,27].

## STATISTICAL ANALYSIS

The data were analysed using SPSS version 10.0. A Student's t-test and Chi-square test were used to assess the association between different categorical variables, while Analysis of Variance (ANOVA) was applied to observe the significance of differences in normally distributed data. A probability value of less than 0.05 was considered significant.

## RESULTS

The study included 100 participants, consisting of 50 prehypertensive patients and 50 controls, including 64 men and 36 women, with a mean age of 46±7 years. The baseline characteristics of the study participants in the two groups are shown in [Table/Fig-1].

| Parameters | | Mean | Std. Deviation | p-value |
|---|---|---|---|---|
| Age (in years) | Case | 46.78 | 7.394 | 0.62 |
| | Control | 46.42 | 7.250 | |
| Height (cm) | Case | 161.86 | 6.395 | 0.001 |
| | Control | 156.30 | 8.157 | |
| Weight (kg) | Case | 66.46 | 7.794 | 0.006 |
| | Control | 61.96 | 8.079 | |
| BMI (kg/m$^2$) | Case | 25.46 | 2.510 | 0.555 |
| | Control | 25.16 | 2.494 | |
| Waist circumference (cm) | Case | 89.96 | 14.774 | 0.014 |
| | Control | 82.20 | 16.132 | |
| Hip circumference (cm) | Case | 98.46 | 13.436 | 0.048 |
| | Control | 92.32 | 16.981 | |
| Urine albumin (mg/L) | Case | 69.18 | 19.831 | 0.001 |
| | Control | 18.72 | 6.230 | |
| PAI-1 (ng/mL) | Case | 14.24 | 3.530 | 0.013 |
| | Control | 12.48 | 3.412 | |
| Total cholesterol (mg/dL) | Case | 197.70 | 14.029 | 0.001 |
| | Control | 115.06 | 11.331 | |
| Triglycerides (mg/dL) | Case | 198.08 | 26.864 | 0.001 |
| | Control | 125.44 | 14.839 | |
| HDL (mg/dL) | Case | 45.00 | 8.894 | 0.001 |
| | Control | 59.64 | 9.833 | |
| LDL (mg/dL) | Case | 129.48 | 13.570 | 0.001 |
| | Control | 94.08 | 14.882 | |
| SBP (mmHg) | Case | 132.10 | 3.297 | 0.001 |
| | Control | 118.04 | 6.803 | |
| DBP (mmHg) | Case | 83.36 | 4.525 | 0.001 |
| | Control | 76.04 | 3.801 | |

**[Table/Fig-1]:** Shows the biochemical and anthropometric characteristics in individual with prehypertensive patients and normotensives.
Test: Student t-test and Chi-square, p<0.05* statistically significant, p<0.001 statistically highly significant; BMI: Body mass index; AI-1: Plasminogen inhibitor-1; DL: High density lipoprotein; DL: Low density lipoprotein; BP: Systolic blood pressure; BP: Dystolic blood pressure

PAI-1 levels were significantly higher in the prehypertensive group compared to the control group (p-value=0.013), although the marker was within the normal range. Participants with higher plasma PAI-1 had significantly higher blood pressure (p-value=0.001) at baseline than those with lower PAI-1. The mean age of prehypertensives with higher plasma PAI-1 was 46.78 years (p-value=0.62), BMI was 25.46 kg/m$^2$ (p-value=0.555), waist circumference was 89.96 cm (p-value=0.014), and hip circumference was 98.46 cm (p-value=0.048). Total cholesterol, triglycerides, and LDL cholesterol

were significantly higher in prehypertensives (p-value=0.001), while HDL cholesterol was significantly lower (p-value=0.001). The study also observed that urine albumin was significantly elevated in the prehypertensive group with increased PAI-1 compared to controls (p-value=0.001).

The present study revealed that elevated plasma PAI-1 did not show a significant and positive correlation with Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) (r=0.138 and 0.66, p-value of 0.338 and 0.648) in the prehypertensive group, as shown in [Table/Fig-2].

| PAI-1 (ng/mL) | Total cholesterol (mg/dL) | Triglycerides (mg/dL) | HDL (mg/dL) | LDL (mg/dL) | SBP (mmHg) | DBP (mmHg) | Urine albumin (mg/L) |
|---|---|---|---|---|---|---|---|
| Pearson correlation | 0.145 | 0.207 | 0.021 | -0.068 | 0.138 | 0.660 | -0.225 |
| p-value | 0.315 | 0.150 | 0.882 | 0.640 | 0.338 | 0.648 | 0.117 |

**[Table/Fig-2]:** To show the correlations between the various parameters in prehypertensive patients.

Plasma PAI-1 was weakly correlated with total cholesterol (r=0.145, p-value 0.315), LDL cholesterol (r=-0.068, p-value 0.640), HDL cholesterol (r=0.21, p-value 0.882), and triglycerides (r=0.207, p-value 0.150) in prehypertensives. Increased PAI-1 did not show any significant correlation with urine albumin (r=-0.225, p-value of 0.117) in the prehypertensive group. Such correlations were not observed in the control groups.

## DISCUSSION

PAI-1 levels were used to evaluate the fibrinolytic activity in prehypertensives. An important finding in the current study is the elevated PAI-1 in prehypertensives, which can significantly contribute to the development of future hypertension and its complications. This finding is consistent with the study conducted by Wang TJ et al., which examined the association of plasma PAI-1 with incident hypertension among 1456 European whites in the Framingham offspring study and found that high PAI-1 levels contribute to the development of hypertension and its complications [28].

Ferguson TS et al., explained in their study that prehypertension is associated with a three-fold increase in the incidence of hypertension. Plasma PAI-1 may contribute to the development of hypertension by affecting vascular remodeling, reducing vessel wall elasticity, and increasing peripheral resistance [29].

Studies have shown impaired fibrinolytic activity in hypertensives, along with defects in coagulation, platelet function, and endothelial dysfunction. All of these factors may predispose individuals to a hypercoagulable state in hypertension, which can play a role in the pathogenesis and complications of hypertension [29-31].

The significantly higher waist circumference in the prehypertension group, which is a known risk factor, is consistent with the studies conducted by Rao KVM and Reddy GPK and Nkeh-Chungag BN et al., who also reported an association between waist and hip circumferences and the presence of hypertension and prehypertension in young South African adults [32,33]. This suggests that waist circumference is a better measure of cardiovascular disease risk compared to BMI, as waist circumference can be influenced by subcutaneous or visceral fat [32,33]. The study did not observe a significant difference in BMI between the two groups, whereas Ferguson TS et al., in their work on the progression from prehypertension to hypertension in a Jamaican cohort, reported that higher BMI can independently predict the development of hypertension [34].

In the present study, total cholesterol, triglycerides, and LDL cholesterol were significantly increased, while HDL cholesterol was low in the prehypertensive group. This finding is consistent with the study conducted by Mishra S et al., which showed a total prevalence of dyslipidemia of 17.4% and higher prevalence of hypercholesterolemia in prehypertensives. Karasek D et al., also explained that the prevalence of prehypertension was higher in patients with dyslipidemia [35,36]. A population study in China involving 1154 subjects found that total cholesterol and triglycerides were significantly higher in prehypertensives compared to normotensives. Studies have reported that increased cholesterol levels can upregulate the expression of PAI-1 due to vascular injury, which could potentially explain the findings in the present study as well [37,38].

It was also observed in the current study that urine albumin was significantly elevated in the prehypertensive group compared to controls (p-value=0.001). Previous studies have also shown a close relationship between PAI-1 levels and the degree of albuminuria [39].

Regarding the correlation between variables, the present study showed no significant correlation between elevated PAI-1 levels and SBP and DBP in prehypertensives, which could potentially be attributed to prehypertension being an incidental finding during the participants' hospital visits.

The study showed that elevated plasma PAI-1 demonstrated a weak correlation with total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol, and urine albumin in prehypertensives. This weak correlation could possibly be due to the small study population. Larger populations and patient follow-ups are required to yield significant results, as explained by Peng H et al., [30]. Sahay S et al., showed in their study that PAI-1 significantly correlated with triglyceride (r=0.492, p-value=0.001), LDL (r=0.604, p-value <0.001), and inversely correlated with HDL (r=-0.392, p-value=0.005) [38]. Additionally, the influence of PAI-1 on the pathophysiology of prehypertension and dyslipidemia is complex and not clearly established. It may depend on genetic, environmental, and vascular interactions. Some prospective studies have also shown that dyslipidemia can strongly predict the occurrence of hypertension over the years [39-41].

This study could assist clinicians in early intervention, and prehypertensive individuals should be targeted for lifestyle modifications or other interventions to reduce the risk of cardiovascular disease. The study may contribute as a potentially valuable tool for a prospective pathophysiological diagnostic panel.

### Limitation(s)

A major limitation of the study is the small sample size. The research needs to be extended to a larger population, and prehypertension being an incidental finding during the participants' hospital visit should be taken into consideration. Although blood pressure was significantly elevated, a follow-up of these participants for at least four to five years is required to obtain significant results. Additionally, other potential predictors of blood pressure, such as gender differences, socio-economic status, physical activity, and dietary factors, could be included in future studies.

## CONCLUSION(S)

PAI-1 is a potential biomarker of impaired fibrinolysis. The main finding of the present study is that plasma PAI-1, total cholesterol, triglycerides, LDL cholesterol, and urine albumin were significantly increased in prehypertensives, suggesting vascular damage and inflammation. Waist circumference and hip circumference were also significant predictors for the development of hypertension and its complications. As prehypertension is usually asymptomatic, lack of awareness and delays in seeking healthcare facilities may increase the risk of developing hypertension and its complications. This study may help primary care physicians identify the risk and prevent further cardiovascular complications.

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