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Original Article

Biochemistry Section

Correlation of Serum Plasminogen Activator Inhibitor-1 with Body Mass Index and Blood Pressure among Newly Diagnosed Primary Hypertensive Patients: A Cross-sectional Study

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ABSTRACT

Introduction: Plasminogen Activator Inhibitor-1 (PAI-1), a serine protease inhibitor expressed in adipose tissue, causes inflammation in hypertension and vice versa. The excess adipose tissue increases the production of PAI-1. There have been no relevant studies conducted on PAI-1 in southern Odisha in relation to Body Mass Index (BMI) and hypertension.

Aim: To compare the BMI, Waist Hip Ratio (WHR), Waist Circumference (WC), and serum levels of PAI-1 in hypertensive cases with controls, and also to correlate the serum level of PAI-1 with BMI and blood pressure.

Materials and Methods: This cross-sectional study was conducted in the Department of Biochemistry in collaboration with the Department of Medicine of MKCG Medical College and Hospital, Berhampur, Odisha, India from November 2020 to August 2021. A total of 45 newly diagnosed primary hypertensive patients and 43 healthy age and sex-matched individuals between the ages of 18 to 60 years were enrolled in the study. Serum PAI-1 was measured by Enzyme-Linked Immunosorbent Assay (ELISA). BMI, WC, hip circumference, WHR, and blood pressures of the controls as well as cases were recorded. Data were statistically analysed using the Student's t-test and Pearson's correlation coefficient.

Results: The proportion of males was higher (56%) than females (44%). The cases had a significantly higher level of serum PAI-1 (203.36 ng/mL) compared to the control group (60.11 ng/mL) (p-value <0.001). The cases had a higher BMI, WC (meters), and WHR compared to the control group. The serum PAI-1 level positively correlated with Systolic Blood Pressure (SBP) (r-value=0.852, p-value <0.001), Diastolic Blood Pressure (DBP) (r-value=0.726, p-value=0.000), BMI (r-value=0.620, p-value=0.001), WC (r-value=0.444, p-value=0.002), and WHR (r-value=0.593, p-value <0.001).

Conclusion: A high serum PAI-1 level was found in the newly diagnosed hypertensive cases, and a significant positive correlation was observed between PAI-1 and systolic and diastolic blood pressure, along with BMI, WC, and WHR.

Keywords: Adipose tissue, Obesity, Serine protease inhibitor, Waist hip ratio

INTRODUCTION

Hypertension, the most common preventable non communicable disease with a multifactorial origin, is a serious medical condition that significantly increases the risk of heart attack, stroke, kidney failure, and blindness [1]. Essential, primary, or idiopathic hypertension is defined as high BP (>130/90 mmHg) in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other causes of secondary hypertension or mendelian forms (monogenic) are not present [2]. National Family Health Survey (NFHS-4) data depicts the prevalence of hypertension in India as 22.4% [3]. Worldwide, raised blood pressure causes 7.5 million deaths, i.e., 12.8% of all deaths [4]. One of the global targets for non communicable diseases is to reduce the prevalence of hypertension by 25% by 2025 and by 33% by 2030 (baseline 2010) [1,5]. There are several predisposing factors like BMI, abdominal obesity, tobacco use, alcohol consumption, smoking, and physical inactivity that are significantly associated with hypertension [6]. Inflammation is a biologically complex response of the human body to harmful stimuli and an important contributor to the genesis of hypertension, leading to target organ damage [7]. Inflammation promotes hypertension by endothelial dysfunction, which contributes to increased systemic vascular resistance. Raised PAI-1 in hypertension due to an inflammatory state causes an imbalance between plasminogen and PAI-1, leading to a hypercoagulable state that leads to cardiovascular events in primary hypertension [8].

The severity of the inflammatory state is measured with the help of various biomarkers like C-Reative Protein (CRP), Tumour Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6). Serum PAI-1 is one of the markers of inflammation [9].

PAI-1 is a serine protease inhibitor mainly produced by endothelial cells, vascular smooth muscle cells, and hepatocytes [10]. In vascular tissue, PAI-1 promotes the accumulation of extracellular matrix and regulates vascular remodeling and perivascular fibrosis. In a study conducted by Peng H et al., the relationship between plasma PAI-1 and incident hypertension showed a significant predicted risk of arterial stiffness, atherosclerosis, and cardiovascular events, all of which have been associated with hypertension [11]. PAI-1 positively correlated with measures of conduit artery stiffness, i.e., mean arterial pressure, central pulse pressure. PAI-1 levels were positively associated with intima media thickness [12]. Arterial stiffness leads to impairment in arterial dilatation capacity and is associated with an increased risk of essential hypertension [13]. Obesity is currently considered a low-grade inflammatory state and is responsible for a series of inflammatory cytokines (in particular, IL-6 and TNF-α) able to induce the overexpression of PAI-1 [14,15].

Also, upon review of the literature, no relevant study was found on the association of PAI-1 with BMI and hypertension in southern Odisha. Hence, the present study was conducted to compare the BMI, WC, WHR, and PAI-1 in hypertensive cases and healthy controls and also to correlate the serum level of PAI-1 with BMI, SBP, DBP, WC and WHR.

MATERIALS AND METHODS

This cross-sectional study was carried out in the Department of Biochemistry in collaboration with the Department of Medicine, MKCG Medical College and Hospital, Berhampur, Odisha, India from November 2020 to August 2021. Approval from the institutional ethical review committee was obtained before conducting the study (IEC no: 905/IEC).

Inclusion criteria: Newly diagnosed cases of primary hypertension from the Department of Medicine aged between 18 to 60 years were enrolled as cases and age, sex-matched normotensive participants were selected as controls.

Exclusion criteria: Patients <18 years and >60 years, diabetes mellitus, acute and chronic inflammatory disease, autoimmune diseases, stroke, smokers, and alcoholics, secondary hypertension were excluded from the study as in these conditions there is an associated inflammation which may affect the level of PAI-1 to some extent [16].

Sample size: Participants for this study were sourced from both the inpatient and outpatient Department of Medicine at MKCG Medical College and Hospital after approval by the ethical committee and obtaining written consent. The researcher visited the outpatient and inpatient department once a week and employed convenient sampling to enroll participants who met the selection criteria as per Joint National Committee (JNC) VII guidelines [17].

Amid the challenges presented by the ongoing COVID-19 pandemic, a total of 45 newly diagnosed primary hypertensive cases from the Department of Medicine were successfully enrolled as group 1 for the study. For each group 1 participant, an age, sex-matched normotensive group 2 participant was selected to ensure comparability. The impacts of the pandemic were acknowledged and managed to ensure participant safety and data quality.

Data collection: A brief history like age, gender, diet, salt intake, exercise, family history, etc., was collected from both cases and controls through a preformed structured questionnaire. BMI was calculated taking body weight (in kilograms) divided by the square of height (in meters) [18]. WC and hip circumference were measured and based on the data, WHR was calculated for each participant of the study. Blood pressures of the controls as well as cases were recorded using a manual sphygmomanometer.

Collection of blood sample: A total of 5 mL of whole blood was collected from each participant under aseptic precautions. 2 mL of blood for plasma was taken for the estimation of fasting plasma glucose and 3 mL of blood for serum was taken for the PAI-1 estimation. An aliquot of 3 mL serum from all samples collected was stored at -20°C for the estimation of serum PAI-1 by ELISA kit. The serum sample was brought to room temperature before starting the assay. Two samples from the control group were discarded due to improper sampling, making the control group 43 instead of 45.

ELISA method for the estimation of PAI-1: Estimation of serum PAI-1 was done by the commercial kit available from BioVendor Human PAI-1 ELISA Kit, Catalogue No: RAF083R, 96T ELISA for Quantitative Detection of serum PAI-1. This enzyme immunoassay technique uses two highly specific monoclonal antibodies, i.e., the anti-Human PAI-1 coating antibody and biotin-conjugated anti-Human PAI-1 antibody [19]. The cut-off value was taken to be ≥83 ng/mL.

STATISTICAL ANALYSIS

Statistical analysis of the data was done using the Statistical Package for Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Comparison between cases and controls was done by the Student's t-test. Correlation between various parameters was derived using the Pearson's correlation coefficient. The software, namely Microsoft Word and Excel, has been used to generate graphs, tables, etc. The statistical significance was determined at a probability level of <0.05.

RESULTS

In the present study, a total of 88 participants (45 in group 1 and 43 in group 2) were included. In the study, in group 1 and 2, the number of male participants was found to be more than female participants. In group 1, the number of participants was higher when taking the history of extra salt intake, non-veg diet, and family history of hypertension as compared to group 2. The number of overweight and obese participants in group 1 was found to be more as compared to group 2, and the number of normal-weight participants was found to be higher in group 2 as compared to group 1 [Table/Fig-1].

Parameters	Frequency	Group 1	Group 2	p-value
Gender	Male	25	24	0.980
	Female	20	19	
Extra salt intake	Yes	18	11	0.150
	No	27	32	
Diet	Veg	08	12	0.257
	Non veg	37	31	
Exercise (150 min/wk)	Yes	11	19	0.050
	No	34	24	
Family H/o hypertension	Present	16	05	0.008
	Absent	29	38	
BMI	Low weight (<18.5)	02	00	<0.001
	Normal (>18.5-24.9)	04	25	
	Overweight/obese (≥25.0)	39	18	

[Table/Fig-1]: Baseline data of all the study participants.

There was no statistically significant difference in age found between the two study groups The mean BMI, WC, HC, WHR in group 1 was found to be significantly higher than in group 2 [Table/Fig-2].

Parameters	Group 1 (N=45)	Group 2 (N=43)	t-value	p-value
Age (Years)	45.33±10.39	42.69±12.97	-1.054	0.295
BMI (Kg/m^2)	28.67±2.61	24.17±2.77	-7.825	<0.001
SBP (mm Hg)	157.95±13.29	126.55±6.47	-13.983	<0.001
DBP (mm Hg)	94.80±8.58	81.44±5.86	-8.486	<0.001
HC (cm)	1.02±0.08	0.92±0.08	-5.317	<0.001
WC (cm)	100.0±9.0	83.0±10.0	-7.520	<0.001
WHR	0.97±0.05	0.90±0.07	-5.354	<0.001

[Table/Fig-2]: Anthropometric and clinical data.
Students t-test

Serum PAI-1 level ranged from 101.50-326.20 ng/mL in group 1 and, in group 2, it ranged from 23.90-80.10 ng/mL and the difference was statistically significant (p-value <0.001) [Table/Fig-3].

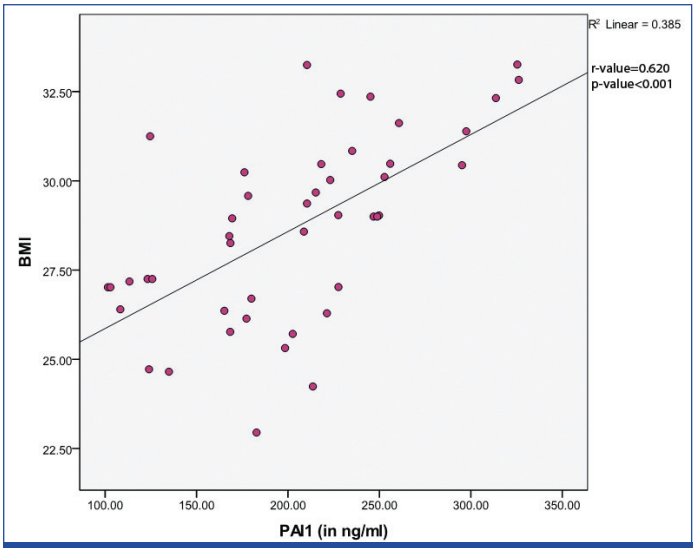
Group	Range (ng/mL)	Mean±SD (ng/mL)	p-value
Group 1 (N=45)	101.50-326.20	203.36±59.64	<0.001
Group 2 (N=43)	23.90-80.10	60.11±12.93	

[Table/Fig-3]: Level of PAI-1 in group 1 and group 2.
Students t-test

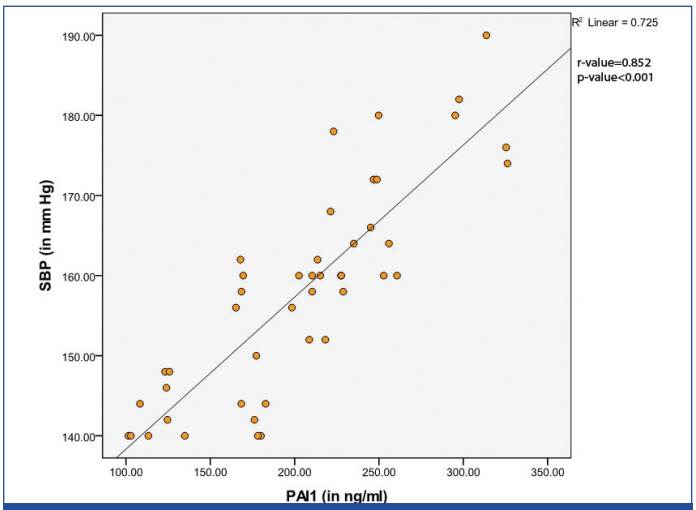
In the present study, a positive correlation of PAI-1 with BMI, SBP, DBP, WC and WHR was found [Table/Fig-4-9].

	PAI-1	
Risk factors of hypertension	r-value	p-value
BMI	0.620	<0.001
SBP	0.852	<0.001
DBP	0.726	<0.001
WC	0.444	0.002
WHR	0.593	<0.001

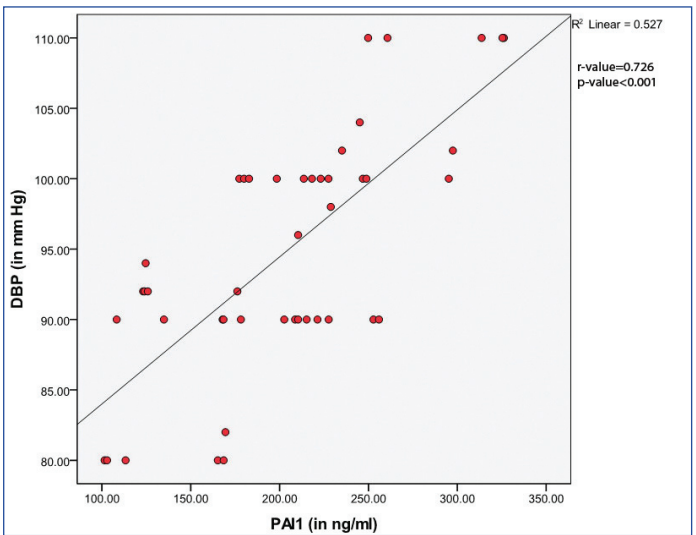
[Table/Fig-4]: Correlation of PAI-1 level with blood pressure and BMI.
Pearson's correlation coefficient



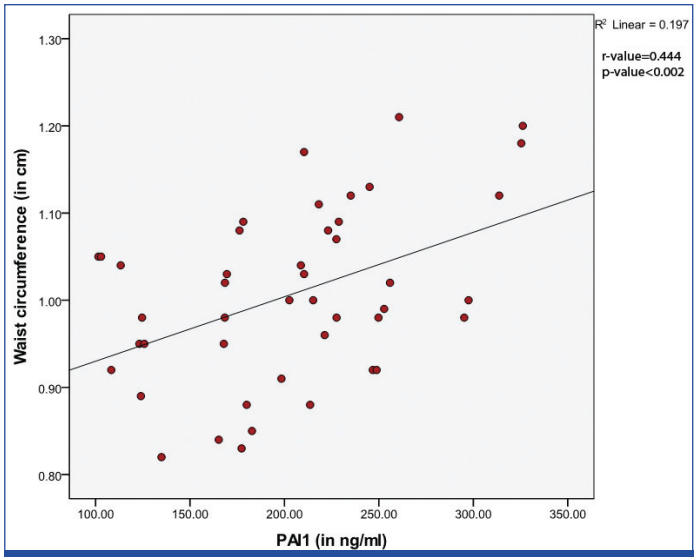
[Table/Fig-5]: Correlation between BMI and PAI-1.



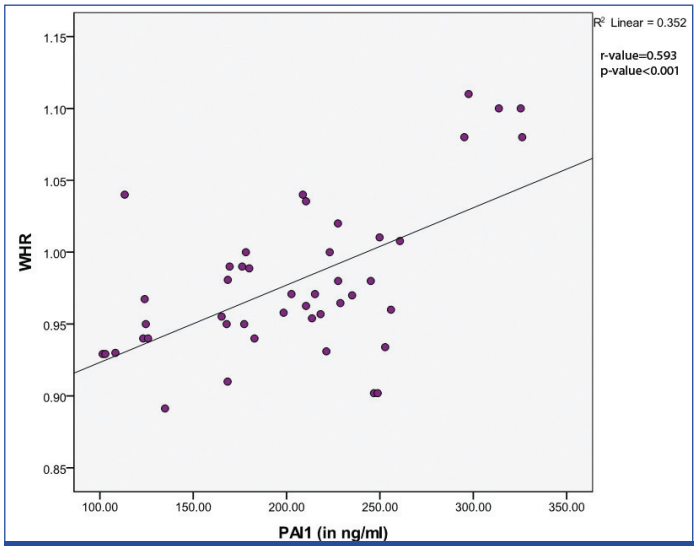
[Table/Fig-6]: Correlation between SBP and PAI-1.



[Table/Fig-7]: Correlation between DBP and PAI-1.



[Table/Fig-8]: Correlation between WC and PAI-1.



[Table/Fig-9]: Correlation between WHR and PAI-1.

DISCUSSION

In the present study, it was observed that anthropometric parameters like BMI, WC, WHR, and clinical parameters like SBP and DBP were significantly higher in group 1 compared to group 2 with a statistically significant p-value of <0.001. Similar studies conducted by Choudhury KN et al., Choi JR et al., and Li Al et al., in found significantly higher BMI in the hypertensive group than in the controls [20-22]. Choudhury KN et al., and Lashkardoost H et al., found WC was also significantly higher in the hypertensive group [20,23]. Choi JR et al., and Lashkardoost H et al., also showed that WHR was significantly (p-value <0.0001) higher in the hypertensive group than the control group [21,23].

In the present study, the mean serum PAI-1 concentration in hypertensive patients was higher than the controls with a statistically significant p-value of <0.001. Peng H et al., [11] in a cohort study showed that a higher level of plasma PAI-1 was associated with an increased risk of developing hypertension. In this study, two longitudinal cohorts were divided into three groups according to the level of PAI-1; low (5-32 ng/mL), intermediate (33-57 ng/mL), and high (58-441 ng/mL). The high PAI level in serum is consistent with present study.

In the present study, there was a positive correlation of PAI-1 with BMI, WC, WHR, SBP, and DBP, which was statistically significant. According to Tjärnlund-Wolf A et al., the concentration of PAI-1 in human plasma varies from a few nanograms per milliliter in a young healthy population to >100 ng/mL in an obese population [24]. Mira MF et al., a cross-sectional study conducted on 43 obese children were compared with age and sex-matched healthy controls of normal BMI found that the obese group had significantly higher PAI-1 levels than the control group [25]. Li A-L et al., and Mira MF et al., also showed a positive correlation between BMI and PAI-1 [22,25]. Wei Y et al., found a positive correlation between WC and PAI-1, and Mira MF et al., showed a positive correlation between PAI-1 and WHR, which is similar to present study [25,26]. Mira MF et al., found a positive correlation of PAI-1 with SBP and DBP [25]. The findings of this study are very similar to present study.

PAI-1 is produced by a variety of cell types such as endothelial cells, adipocytes, hepatocytes, leukocytes (monocytes and macrophages), megakaryocytes, and platelets. A number of factors induce PAI-1 synthesis and secretion. PAI-1 synthesis is augmented by proinflammatory cytokines such as Transforming Growth Factor beta (TGF-β), TNF-α, and IL-6. PAI-1 expression is stimulated by CRP, glucose, insulin, thrombin, and angiotensin II. Plasminogen activation is inhibited by PAI-1, and active PAI-1 acts as a suicide substrate for urokinase type and tissue type plasminogen activator by forming a covalent complex [27]. PAI-1 plays a critical role in the regulation of endogenous fibrinolytic activity and resistance to thrombolysis. It also inhibits cellular migration [28] and matrix degradation [29] in vascular tissues in response to injury. Excess PAI-1 exacerbates the development of fibrosis in some animal models [30,31]. The plasminogen activator system regulates vascular cell growth and remodelling as a result of plasmin-dependent processing of chemokines and cytokines such as basic fibroblast growth factor, TNF-α, monocyte chemotactic protein-1, TGF-β, and IL-1 [32]. Therefore, PAI-1 may likely block the proteolytic pathways critical to the maintenance of high blood pressure and hypertension-associated arteriosclerosis [33].

Limitation(s)

The present study did not evaluate inflammatory markers like CRP, IL-6, TNF-α. The sample size of the present study was small and was enrolled using convenient purposeful sampling.

CONCLUSION(S)

The mean BMI, SBP, DBP, and PAI-1 were found to be higher in cases compared to controls, and a positive correlation was found between PAI-1 and BMI, SBP, and DBP. This suggests that serum PAI-1 may be implicated in the pathogenesis of hypertension, as there is an identified link between PAI-1 and blood pressure. The results of the present study imply that the measurement of serum PAI-1 can be conducted in a large clinical setting to predict the risk of developing major cardiovascular events. Determining serum levels of PAI-1 may help obtain prognostic information following the treatment of hypertension. Further large-scale studies should be performed to validate these concepts and to translate them to clinical practice, using these parameters independently or in combination with risk factors, for the risk assessment of essential hypertension.

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