

## Association of Hypertension with Raised Serum Homocysteine Levels

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### ABSTRACT

**Objective:** To study the association of hypertension with raised serum homocysteine levels.

**Study Design:** Comparative cross-sectional study.

**Place and Duration of Study:** Army Medical College Rawalpindi in collaboration with Armed Forces Institute of Pathology and Military Hospital Rawalpindi, from Mar to May 2021.

**Methodology:** Total study participants were four hundred in number. Two hundred patients with hypertension aged between 35-55 years were included in Group-1, whereas two hundred non-hypertensive patients with the closest possible age and sex matching were included in Group-2. Strict adherence to inclusion and exclusion criteria was ensured.

**Results:** The mean age of patients with hypertension (Group 1) was  $42.60 \pm 9.95$  years, and without hypertension, i.e., healthy participants (Group 2), was  $42.26 \pm 10.03$  years. Systolic BP was  $157.92 \pm 8.07$  mmHg among Group 1 (hypertensive subjects) and  $114.60 \pm 4.58$  mmHg among Group 2 (healthy participants). Mean diastolic blood pressure in patients with hypertension (Group 1) was  $104.95 \pm 5.87$  mmHg, whereas it was  $74.20 \pm 4.74$  mmHg among non-hypertensive healthy participants (Group 2). Mean serum homocysteine level was significantly correlated with hypertension ( $p$ -value  $<0.001$ ,  $r=0.804$  for systolic and  $p$ -value  $<0.001$ ,  $r=0.792$  for diastolic blood pressure) and was higher in Group 1 ( $20.64 \pm 4.40$   $\mu\text{mol/L}$ ) than that of healthy Group 2 ( $9.48 \pm 2.38$   $\mu\text{mol/L}$ ).

**Conclusion:** Our study concludes that serum homocysteine had a significant positive correlation with hypertension and can be used as an early marker for hypertension assessment in addition to regular blood pressure measurements.

**Keywords:** Diastolic pressure, Hyper-homocysteinemia, Hypertension, Systolic pressure.

**How to Cite This Article:** Ikram H, Jaffar SR, Hayat A, Khattak M, Ellahi A, Naeem A. Association of Hypertension with Raised Serum Homocysteine Levels. *Pak Armed Forces Med J* 2022; 72(3): 1125-1129. DOI: <https://doi.org/10.51253/pafmj.v72i3.7219>

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## INTRODUCTION

Hypertension is one of the most important chronic conditions of global concern. It has a major contribution to the disease burden worldwide.<sup>1</sup> At first, its relationship with risk factors and other etiologies was not established.<sup>2</sup> Due to the increased association of hypertension with cardiovascular diseases and other systemic ailments, it is difficult to conclude when one disease or factor becomes a risk factor for the other.<sup>1,2</sup>

Different risk factors and biomarkers are being studied worldwide. Some of these may be essential for the early prediction/diagnosis of hypertension. Still, other markers on which research is going on include markers regarding prognosis and risk stratification of patients into various disease categories and subsequent referral of patients to different departments in the hospital.<sup>3,4</sup> This also includes high-risk patients who may die if not treated on an urgent basis. Homocysteine is one such marker. Although its role in patients

suffering from hypertension is yet to be fully elucidated, it has been recognized as one of the risk factors for hypertension.<sup>4</sup> Different studies and research on hypertension have clearly described how homocysteine affects vascular endothelium.<sup>4,5</sup> These mechanisms include arteriolar constriction, increased arterial stiffness, renal dysfunction and increased sodium reabsorption. The main mechanism by which homocysteine may result in hypertension includes oxidative stress, which results in oxidative injury to vascular endothelium, diminishing action of nitric oxide to cause vasodilatation, stimulating vascular smooth muscle proliferation and altering elastic properties of vessel wall leading to hypertension.<sup>5,6</sup>

The vascular risk is higher in patients with hypertension and hyperhomocysteinemia. This direct relationship has been a focus of some studies. Several epidemiological studies have also indicated a positive association between CVD risk and the modest effect of increased homocysteine levels.<sup>6-8</sup>

More than 70% of individuals with raised serum homocysteine had aortic systolic pressures similar to

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Received: 11 Aug 2021; revision received: 25 Jun 2021; accepted: 30 Nov 2021

those with hypertension. This is because vital organs are exposed to the central rather than the peripheral BP, although this difference is highly variable between individuals.<sup>8</sup> It has also been suggested that a measurement of central systolic blood pressure is a better marker of anti-hypertensive treatment assessment, especially in patients with chronic kidney disease, compared to peripheral systolic blood pressure.<sup>9</sup> Emerging evidence now suggests that central pressure is better correlated with end-organ damage and cardiovascular events than peripheral systolic blood pressure (pSBP). Moreover, anti-hypertensive drugs can exert differential effects on brachial and central pressure. Therefore, cSBP has different physiology and may offer improvements in CVD risk assessment compared to pSBP.<sup>7-9</sup> However, measurement of cSBP is cumbersome, as it requires the use of a central arterial catheter whose insertion is not feasible in every patient, nor is it recommended in all patients with hypertension.<sup>9</sup> Our study excluded patients with significant CKD as a cause of hypertension and focused on essential hypertension and its relationship with hyperhomocysteinemia.

Homocysteine biochemistry needs some elucidation at this point. Homocysteine is an amino acid not used in protein synthesis. Homocysteine, an intermediate produced during the methionine metabolism pathway, is a nonprotein amino acid containing sulfur, which is formed as an intermediate between the trans-sulfuration and remethylation pathway of methionine and cysteine. Its role is to serve as an intermediate in methionine metabolism. Homocysteine is located at a branch point of metabolic pathways: either it is irreversibly degraded via the trans-sulphuration pathway to cysteine or remethylated back to methionine. Its levels decline by administration of folate, which indicates a link between homocysteine and folate metabolism.<sup>6-9</sup>

High homocysteine has been linked to various cardiovascular diseases, including hypertension. It has been observed in a study that around 80% of patients suffering from hypertension had elevated homocysteine levels.<sup>10</sup> Data from this and other studies have suggested that elevated homocysteine is an independent risk factor for hypertension, including pulmonary hypertension. We further investigated this finding in our study.

## METHODOLOGY

The study was conducted after obtaining approval from the Ethical Review Committee (ERC/ID/131) of Army Medical College. In addition, informed consent was obtained from all study participants.

It was a comparative cross-sectional study conducted from March-May 2021 at the Department of Chemical Pathology, Military Hospital Rawalpindi, in collaboration with the Armed forces Institute of Pathology.

**Inclusion Criteria:** Patients aged 30 to 55 years, known non-diabetic and had essential hypertension were included in the study.

**Exclusion Criteria:** Patients with coronary artery disease, diabetes mellitus, significant valvular disease, COPD, CKD, and life-threatening systemic diseases were excluded from the study. In addition, females having pregnancy, using OCP and subjects receiving steroids, anti-depressants and anticonvulsant drugs were also excluded from this study.

The study population consisted of two Groups (Group-1 which included patients with hypertension, and Group 2, which included healthy participants for comparison). Demographic data regarding age and sex were obtained from each patient. Two hundred subjects were included in Group 1 as patients with hypertension, followed by the inclusion of two hundred healthy subjects in Group 2 with age and sex matching as far as possible for comparison. Ethnicity/family history was not considered as a bar on the inclusion of subjects. Subjects from rural and urban settings were included, and socioeconomic status was not considered while including subjects.

The sample size was calculated using an online calculator ([www.calculator.net](http://www.calculator.net)). Prevalence of hypertension was thirty-three percent (33%) as obtained from a study on the Pakistani population.<sup>11</sup> Therefore, a confidence level of 95% and a margin of error of 5% were used for sample size calculation. As calculated, the sample size was 340, and we took a sample size of 400 for the study, which was more than our estimated sample size. Samples were collected using convenience sampling.

Peripheral systolic and diastolic BP was measured by a standard procedure using a mercury sphygmomanometer as given by JNCV II. Central systolic and diastolic blood pressures were not measured due to invasiveness and lack of consent by the patients to use the invasive procedure involved in the measurement of central arterial pressure, that is, insertion of a central arterial catheter. Normal blood pressure was taken to be 120 by 80 millimetres of mercury. Patients with almost all grades of hypertension were studied. Serum homocysteine was measured for both Groups. Homocysteine was measured using an automated chemistry

analyzer Abbot Architect 2000. Various cutoffs were studied for use in the study with different sensitivity and specificity for detection of the association of hypertension with raised homocysteine. The selected range included normal homocysteine up to 15 micromol/litre.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis and Microsoft Excel were used in data compilation. The significance level was determined using an independent sample t-test, and the *p*-value <0.05 was taken to be statistically significant.

**RESULTS**

Our study comprised two Groups (Group 1 included 200 patients with hypertension, and Group 2 included 200 healthy participants). Group 1 and Group 2 further consisted of 65 (32.5%) and 64 (32%) females and, 135 (67.5%) and 134 (67%) males respectively. The mean age of Group 1 subjects was 42.60 ± 9.95 years, while in Group-2, it was 42.26 ± 10.03 years. Values of blood pressure and homocysteine Wwere summarized in Table-I.

**Table-I: Age, systolic and diastolic blood pressure and homocysteine levels in Study Groups.**

Parameters	Group 1 (Mean ± SD) n=200	Group 2 (Mean ± SD) n=200
Age (years)	42.60 ± 9.95	42.26 ± 10.03
Systolic BP (mmHg)	157.92 ± 8.07	114.60 ± 4.58
Diastolic BP (mmHg)	104.95 ± 5.87	74.20 ± 4.74
Homocysteine (micromol/liter)	20.64 ± 4.40	9.48 ± 2.38

Raised homocysteine levels in blood were significantly associated with hypertension (*p*-value <0.01).

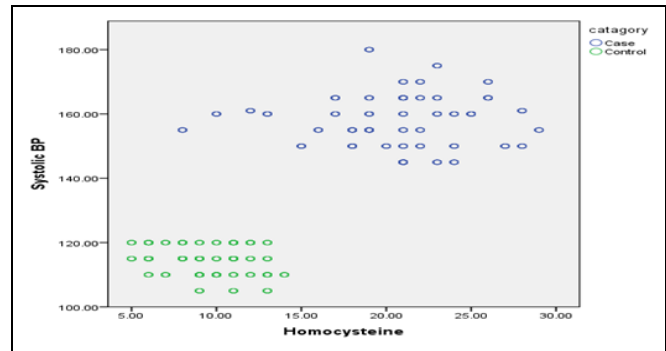
Further, Pearson correlation was applied to test the systolic and diastolic blood pressure relationship with homocysteine levels (Table-II).

**Table-II: Pearson correlation for systolic and diastolic blood pressure and homocysteine.**

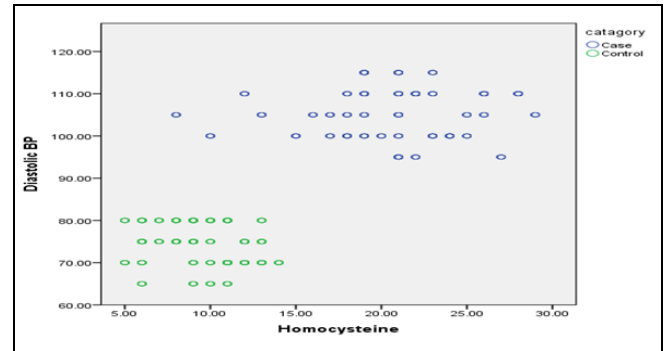
		Homocysteine
Systolic BP	Pearson Correlation	0.804
	<i>p</i> -value	<0.001
Diastolic BP	Pearson Correlation	0.792
	<i>p</i> -value	<0.001

Figure-1 and Figure-2 showed the distribution of homocysteine levels in both Groups separately for comparison with systolic and diastolic blood pressure in separate figures. Figures illustrated that high homocysteine levels are associated with increased blood pressure among patients suffering from hypertension,

both systolic and diastolic blood pressures, compared to healthy participants.



**Figure-1: Distribution of homocysteine levels in Group-1 and Group-2 for comparison with systolic blood pressure.**



**Figure-2: Distribution of homocysteine levels in Group-1 and Group-2 for comparison with diastolic blood pressure.**

**DISCUSSION**

The major finding in our study was a positive association between high blood pressure, i.e., both systolic and diastolic blood pressure, with high homocysteine levels in the blood.

The association between high blood pressure and raised homocysteine levels has previously been demonstrated by various studies using brachial blood pressure measurement, i.e., peripheral blood pressure.<sup>12,13</sup>

In our study mean age was 42.60 ± 9.95 in Group 1 and 42.26 ± 10.03 years in Group 2. Males constituted a major chunk of the Group 1. Advancing age, although is known as a non-modifiable risk factor for atherosclerosis, subsequent hardening of vessels and hypertension, in our study, it was observed not to be linked as a cause of raised blood pressure as signified by increased age of healthy Group 2 participants and younger age of Group 1 participants (patients of hypertension). This is against the common observation, although other studies support it. For example, in a study carried out by Korzeniowski *et al*, it was observed that

18 patients suffering from hypertension and 15 normotensive subjects had a mean age of  $43 \pm 16$  years and  $47 \pm 10$  years. In their study, also males were predominant, and the effect of age on hypertension incidence was against the common observation, i.e., increasing age is associated with hardening vessels and subsequent development of hypertension. This, however, could be due to chance, as various large multi-center international studies have gone against this observation.<sup>13</sup>

Our study observed that both peripheral measured brachial systolic and diastolic blood pressure were significantly raised in Group 1 compared to Group 2 in all patients with different grades of hypertension, showing a more or less graded increase of homocysteine when linked to hypertension. This graded rise in homocysteine with hypertension was an observation which has also been established by various other studies which support our findings.<sup>13,14</sup> Our study established a positive association between hypertension and raised serum homocysteine levels when the two Groups were compared.

The European Concerted Action Project also showed that raised serum homocysteine was an independent risk factor for CVD, and they clearly showed that an increase of 5 micromol/L of homocysteine level was associated with an increase in relative risk of CVD of 1.355.<sup>15,16</sup>

Moreover, the link between raised homocysteine above normal reference range and elevated systolic and diastolic blood pressure established in our study has been confirmed in other cross-sectional reports and experimental studies. For example, data from 3,524 school children, including adolescents in a cardiovascular health study, showed that Hcy was independently associated with raised SBP.<sup>17</sup> However, this finding cannot be applied in our study as we took middle-aged people aged from thirty-five to fifty-five years, though it is an important observation/finding that may be generalized to the population at large.

Cross-sectional data from the Third National Health and Nutrition Examination Survey has indicated that one standard deviation (5  $\mu\text{mol/l}$ ) increase in Hcy was associated with increases of 0.5 and 0.7 mmHg in systolic and diastolic blood pressure, respectively, after adjusting for cardiovascular risk factors.<sup>18</sup> A previous study examined a very large sample (16,176 individuals) and reported a weak association of plasma Hcy with SBP and DBP confined to younger individual.<sup>19</sup> This is contrary to our study, which

showed a strong positive association between hypertension and a graded increase in serum homocysteine levels with age. Some studies do not support these findings.<sup>19</sup>

Additionally, raised homocysteine level association with hypertension pathogenesis as a causal agent is further augmented by demonstrating that lowering homocysteine levels via treatment is associated with a reduction in both systolic and diastolic blood pressure in patients with hypertension. Various studies reported high homocysteine in patients suffering from hypertension previously and found that folic acid does not improve endothelial function in healthy hyperhomocysteinemia subjects compared to those suffering from hypertension.<sup>20</sup>

Our study supports this observation, and it is indicated from our study that hypertension is associated with high homocysteine levels, and early measurement of homocysteine in patients with hypertension may provide valuable time for early treatment initiation, lowering homocysteine levels in the blood and possibly treating hypertension.

### CONCLUSION

Raised serum homocysteine above the normal reference range is associated with hypertension (both systolic and diastolic) and is an independent cardiovascular risk factor which nutrition, exercise and drugs can modify. Though most research work suggests a relationship, there seems to be other evidence that still prevents its inclusion as a biomarker. Our study provides evidence that homocysteine may play an important role in regulating blood pressure. The author feels that it is necessary to combat the ill effects of hyperhomocysteinemia as it has a pivotal influence on the pathology of hypertension. Larger cross-sectional/prospective and replication studies are required to establish these findings as facts.

**Conflict of Interest:** None.

### Authors' Contribution

HI: Principle investigator, SRJ: Responsible for all aspects, AH: Critical analysis, MK: Data compilation, AE: Statistical analysis, AN: Data analysis.

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## Raised Serum Homocysteine Levels

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