

Association of high blood pressure with raised homocysteine level among urban population- A case control study

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ABSTRACT

Introduction: Hypertension is a major risk factor for cardiovascular diseases. Raised homocysteine level is also an important independent risk factor for CVD. This study sought to determine whether there is any relationship between plasma homocysteine and blood pressure levels.

Method: A case control study was conducted among 200 hypertensive cases and 200 normal healthy control groups. Cases were from the Department of medicine and hypertensive clinics at GMC, Baramati and similar controls were selected from patients' neighborhood. Detailed clinical assessment as well as plasma homocysteine level were assessed and compared in both.

Results: Hypertensive cases had higher mean homocysteine level ($21.3 \pm 4.6 \mu\text{mol/L}$) from controls ($13.0 \pm 6.0 \mu\text{mol/L}$), $p < 0.001$. Homocysteine is positively correlated with both systolic and diastolic blood pressure among both hypertensive patients and healthy controls. In both hypertensive subjects and healthy control, homocysteine level has weak positive correlation with DBP and moderate to strong positive correlation with SBP. The hypertensive cases had very high chance (OR=52.4) of developing hyperhomocysteinemia ($>15 \mu\text{mol/L}$), $p < 0.001$.

Conclusion: This study showed higher mean plasma homocysteine levels in hypertensive subjects than controls. Serum homocysteine concentrations were positively associated with both systolic and diastolic blood pressure levels in a general adult population.

KEYWORDS: Plasma homocysteine, hypertension, Case control, blood pressure.

INTRODUCTION

Over the last 5 decades, as well as presently, the morbidity and mortality attributed to the hypertension continues to be a major public health issue both at the local and global levels. Despite various individual and population-

based efforts to address the traditional and well-known modifiable risk factors that contribute to cardiovascular disease, including hypertension, such as reducing dietary sodium intake, weight reduction, increasing physical activity and cessation of smoking, the disease burden attributable to hypertension and its corresponding target organ damage is on the rise. [1]

Increased levels of plasma homocysteine have been contemplated as an independent risk factor for cardiovascular disease. [2, 3] Specifically, high plasma homocysteine levels are related to increased risk for myocardial infarction, stroke, heart failure and occlusive peripheral arterial disease. [4-8] Furthermore, hyperhomocysteinemia is associated with increased carotid intima and media thickness, extracranial carotid artery narrowing and atherosclerotic changes in coronary arteries. Among the possible mechanisms that these effects are exerted on are increased smooth muscle cell proliferation, endothelial dysfunction, increased collagen synthesis and deterioration of elastic material of the arterial wall. An independent relationship between high homocysteine levels and isolated systolic hypertension are reported, which was attributed to arterial wall stiffening. [9]

More than 70% of individuals with increased serum homocysteine had aortic systolic pressures similar to those with hypertension. This is for the reason that vital organs are exposed to the central rather than the peripheral blood pressure, although this difference is highly variable between individuals. [10] Recent studies have showed that central pressure is better correlated with end-organ damage and cardiovascular events but measurement of central SBP is inconvenient, 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. [11]

On account of this disputation in the earlier reports, the purpose of this study was to assess the relationship between plasma homocysteine levels with arterial hypertension and normotensive controls. Therefore, this study was aimed at determining whether there is a difference in homocysteine

levels between hypertensive subjects and normal healthy controls among urban population.

METHODOLOGY

Study Design: Case Control Study

Study Setting: Known diagnosed cases of essential hypertension from department of medicine and from hypertensive clinics at GMC, Baramati. Healthy controls selected from willing patient escorts and patients' neighborhood. The controls were group matched as per age and sex. The participants were enrolled from Jan 2021 to Sep 2022.

The study was conducted after obtaining approval from the Ethical Review Committee of Government Medical College, Baramati. In addition, informed consent was obtained from all study participants.

Sample Size: Samples were collected using convenience sampling. 200 cases and 200 controls were enrolled as per following criteria.

Inclusion criteria- Hypertensive patients were, adult (aged 30 to 55 years) subjects who had essential hypertension (BP \geq 140/90 mm Hg) were included in the study, with willingness to participate, current use of anti-hypertensive medications and non-diabetes (Fasting blood glucose $<$ 110 mg/dl). Those for healthy controls were non-hypertensive (BP $<$ 140/90 mm Hg), non-diabetes (FBG $<$ 110 mg/dl), willingness to participate without clinical evidence of renal, hepatic or cardio respiratory disease.

Exclusion criteria-Patients with coronary artery disease, diabetes mellitus, significant valvular heart disease, COPD, chronic kidney disease (serum creatinine $>$ 3 g/dl), and life-threatening systemic diseases were excluded from the study. In addition, pregnant females, females using OCP and subjects receiving steroids, anti-depressants and anticonvulsant drugs were also excluded from this study. Also, those with history of current tobacco use; excessive alcohol use; excessive caffeine use; history of heart failure, stroke, transient ischemic attack, heart attack, sickle cell disease or pregnancy; as well as use of drugs known to interfere with homocysteine metabolism such as: methotrexate, anticonvulsants, nitrous oxide, sulfadoxine- pyrimethamine, penicillamine, vitamin supplements and contraceptives.

Clinical and Laboratory Examination: Peripheral systolic and diastolic BP was measured by a standard procedure using a mercury sphygmomanometer as given by JNCV II. Patients with almost all grades of hypertension were studied. Routine blood investigation including serum Urea and creatinine were also measured. Serum homocysteine was measured for both Groups. Homocysteine was measured by using Semiautomatic Erba Chem 5 biochemistry analyzer.

Data Entry and Analysis: Microsoft Excel was used in data compilation. Statistical Package for Social Sciences (SPSS) version 20.0 IBM was used for the data analysis. Mean values were compared using independent sample student t-test

and the p-value $<$ 0.05 was taken to be statistically significant.

RESULT

Total 200 cases of hypertension and 200 health controls were enrolled in the study. Mean age and sex composition of cases and control did not differ significantly, $p>$ 0.05 but Cases had higher mean BMI (23.32 ± 5.39) compared to healthy controls (22.60 ± 4.50), $p<$ 0.001. Similarly, average systolic and diastolic blood pressures were also higher in cases than controls Table 1.

Variables	Hypertensive Cases	Health Control	P value*
Male	109	112	0.75
Female	91	88	
Age (Mean \pm SD)	42.60 \pm 9.95	42.26 \pm 10.03	0.75
BMI (Mean \pm SD)	23.32 \pm 5.39	22.60 \pm 4.50	$<$ 0.001
SBP (Mean \pm SD)	148.11 \pm 6.88	120.69 \pm 7.58	$<$ 0.001
DBP (Mean \pm SD)	94.72 \pm 3.29	79.63 \pm 4.53	$<$ 0.001

SBP:Systolic Blood Pressure; DBP: Diastolic Blood Pressure; n = Number of subjects *Student t test applied for quantitative data.

Table 1: Socio-demographic and clinical characteristics of the study population

Variables	Hypertensive Cases (n=200)	Healthy controls (n=200)	P value
Plasma Homocysteine (μ mol/L)	21.30 \pm 4.59	13.00 \pm 6.05	$<$ 0.001
Fasting glucose level (mg/dl)	101.53 \pm 6.48	97.10 \pm 7.08	$<$ 0.001
Urea(mg/dl)	15.82 \pm 4.94	14.02 \pm 4.25	$<$ 0.001
Creatinine (mg/dl)	1.03 \pm 0.14	0.99 \pm 0.14	$<$ 0.001

Independent Student's t test

Table 2: Laboratory Parameters of the Study Population

Hypertensive cases had higher mean homocysteine level ($21.3 \pm 4.6 \mu$ mol/L) from controls ($13.0 \pm 6.0 \mu$ mol/L),

$p < 0.001$. Figure 1 Additionally, fasting blood glucose level, urea and creatinine level were higher among cases than controls Table 2

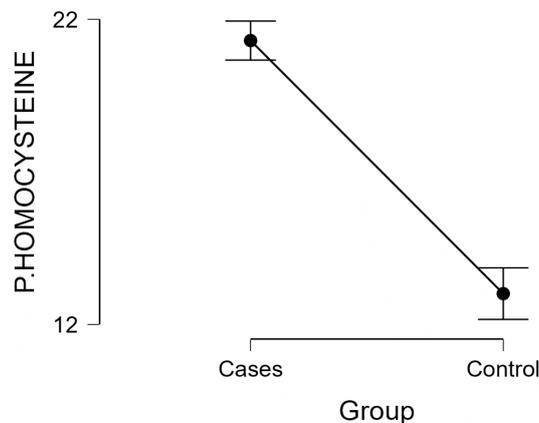


Figure 1: Mean homocysteine level with 95% confidence interval in hypertensive patients & healthy controls.

Homocysteine level (μmol/L)	Hypertensive Cases (n=200)	Healthy control (n=200)	Total
<15	16(8%)	164(82%)	180(45%)
15-30	180(90%)	36(18%)	216(54%)
30-100	4(2%)	0	4(0.01%)
Total	200	200	400

Chi Square test, p value < 0.001.

Table 3: classification of homocysteine level and distribution between normal healthy controls and hypertensive subjects

Furthermore, as in Table 3 there were 184 (92.0%) out of 200 hypertensive subjects with hyperhomocysteinemia. Out of these, 180 (90.0%) had mild hyperhomocysteinemia (15–30 μmol/L), while 4 (2.0%) had moderate hyperhomocysteinemia (30–100 μmol/L) and only 16 (8.0%) hypertensive subjects had normal homocysteine (5–15 μmol/L) levels. There were 164 (82.0%) normal healthy controls with normal homocysteine levels, while 36 (18.0%) had mild hyperhomocysteinemia. There were no control subjects with moderate to severe hyperhomocysteinemia. Raised homocysteine levels in blood were significantly associated with hypertension (p-value < 0.01).

Homocysteine is positively correlated with both systolic and diastolic blood pressure among both hypertensive patients and healthy controls. In both hypertensive subjects and healthy control, homocysteine level has weak positive correlation with diastolic BP and moderate to strong positive correlation with systolic BP among both cases and controls. Hypertensive patients having high homocysteine level 52

times more than compared to control. Table 4

Pearson correlation was applied to test the systolic and diastolic blood pressure relationship with homocysteine level. Homocysteine positively correlated with systolic ($r = 0.63$, $p < 0.001$) and diastolic ($r = 0.35$, $p < 0.001$) blood pressures in hypertensive subjects using the Pearson's Correlation analysis. There was also a significant correlation of homocysteine with systolic ($r = 0.65$, $p < 0.001$) with DBP ($r = 0.58$, $p = 0.03$) in the normal healthy controls.

DISCUSSION

Based on a well-designed epidemiological cohort with a good sample size, the present study may provide powerful evidence of a significant association between homocysteine and hypertension, using cross-sectional analysis. Furthermore, elevated plasma homocysteine levels may be an independent predictor of hypertension, regardless of the study design (cross-sectional or longitudinal) and gender effect.

The relationship between homocysteine and BP has been proposed by several researchers.^[12-14] Plasma homocysteine levels have been identified as a potential bio marker for endothelial dysfunction and have been linked to severe diseases associated with endothelial injury.^[15]

Overall, our findings supported a positive association between homocysteine level and blood pressure in young adults in the conventional observational analysis. Similar to previous studies^[16]. Our finding support that homocysteine concentration is positively associated with SBP and DBP among young adults.

Homocysteine also demonstrated a significant ($p < 0.001$) positive correlation to SBP and DBP in all subjects as well as in the hypertensive subjects when compared to the controls. This signifies that homocysteine might be a risk factor for hypertension.

The high homocysteine levels in the hypertensive subjects ranged from mild to moderate levels with most of the patients having mild homocysteine levels and no subjects with severe hyperhomocysteinemia. On the contrary, the normal healthy controls had just a few subjects with mildly raised homocysteine levels (>15 μmol/L) whereas the majority fell in the normal range.

However, in Framingham Heart Study, no major association was noted between the baseline plasma homocysteine level and hypertension incidence or longitudinal BP progression, after adjustment for age, gender, and other important confounding factors. During the third national health and nutrition in the United States survey a cross-sectional study conducted reinforced the relationship between homocysteine and BP levels, and this correlation seems to be more noticeable in women. A Danish study conducted in the same year showed that the interaction between homocysteine and hypertension was influenced by renal function. In China, Wang and colleagues prospectively traced the BP pro-

Homocysteine level	Hypertensive Cases	Healthy control	Total
High homocysteine level (>15)	184 (92.0%)	36 (18.0%)	220 (55.0%)
Low homocysteine level (<15)	16 (8.0%)	164 (82.0%)	180 (45.0%)
Total	200 (100.0%)	200(100.0%)	400(100.0%)

Pearson's Chi Square test, p<0.001. Odds ratio (OR) =52.3, (95% CI 28.0 – 97.9)

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; n = Number of subjects

Table 4: Association of high homocysteine level with high blood pressure

gression of a normotensive population with different homocysteine levels over a 2-year period. A gender difference, indicating that homocysteine was not a significant risk factor for women was noted. In a study at Liao-Ning, Jiang-Su, and Xin-Jiang provinces found a significant and positive associations of homocysteine concentrations with hypertension and BP. [15]

Abnormal renal function has also been documented to be associated with hyperhomocysteinaemia and high blood pressure levels though with incompletely understood mechanisms and creatine/creatinine production has been shown to be directly associated with S-adenosyl-homocysteine/homocysteine production. Hypertensive subjects in this study showed slightly lower GFR levels than normal healthy controls, however the mean GFR levels were within normal physiologic range in both patients and controls. [17]

Furthermore, slightly higher fasting blood glucose levels in hypertensive patients when compared to healthy controls were noted, however the mean FBG levels of both patients and controls were within normal physiologic range more so as diabetes subjects were excluded ab initio. Few studies have shown association between diabetes and hyperhomocysteinemia and consequently high blood pressure levels. [18, 19]

Despite these important findings, a longitudinal larger population-based studies should be carried out in Maharashtra population across different district to determine whether casual relationship between homocysteine level and blood pressure progression. More variables need to be collected in future studies.

CONCLUSION

Elevated total plasma homocysteine may be used as anticipating biomarker for hypertension. Our findings contribute to the better understanding of the mechanism by which elevated homocysteine effects blood pressure levels, may help to improve hypertension prevention and control, a growing concern in clinical and community settings.

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