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Serum Homocysteine and Serum Lipids in Hypertensive Patients

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Abstract:
Introduction: Over the past 5 decades the morbidity and mortality attributable to hypertension continues to be a major public health issue both at the local and global levels. Of the multiplicity of established risk factors associated with the development of hypertension and its complications (such as heart disease, stroke, chronic kidney disease, accelerated atherosclerosis, and premature death), hyperhomocysteinemia has arguably been one of the most elusive of the proposed risk factors to convincingly link to hypertension. Previous studies established a possible link among hyperhomocysteinemia (HHcy), dyslipidemia, and atherosclerosis. However, there was limited epidemic data concerning the relation between HHcy and lipid profiles, especially in hypertensive patients.
Objective: This study aim to investigate the association of plasma homocysteine (Hcy) level with lipid profiles in hypertensive patients.
Methods: 162 hypertensive patients attending Hi-tech Medical College OPD were evaluated for homocysteine and lipid levels. The patients were divided into groups according to according to homocysteine levels
Results: 34.6% patients had normal homocysteine levels, 37% showed moderate increase and 28.4% patients showed intermediate increase in homocysteine levels. Increased homocysteine levels showed strong association with BMI, waist circumference, BP, diet, smoking and glycemic status. Triglyceride and HDL depicted significant odds ratio (OR) to predict the risk factor for hyperhomoocysteinemia.
Conclusion: The present study showed that hypertensive with HHcy was independently associated with hypertriglyceridemia and low levels of HDL-C, which provides evidence that Hcys levels might affect HDL-C and TG metabolism.

Keywords: *hypertension; hyperhomocysteinemia; dyslipidemia.*

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I. Introduction:

Hyperhomocysteinemia (HHcy) has been regarded as a new modifiable risk factor for cardiovascular disease (CVD) through various mechanisms, including vascular endothelium damage, stimulation of smooth muscle cell proliferation, enhanced low-density lipoprotein cholesterol (LDL-C) peroxidation and thrombosis activation [1, 2]. Previous studies also established that there was a possible link among HHcy, dyslipidemia and atherosclerosis. Regarding Hcy, an inverse association between this amino acid and lipoproteins, especially high-density lipoprotein cholesterol (HDL-C), has been well described in humans and various animal models of HHcy [3]. HHcy might also increase the risk of CVD in dyslipidemia patients [4–6]. Although the mechanism of the link is not thoroughly known, recent studies strongly demonstrated the importance of the metabolic balance between S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), phosphatidylcholine (PC), phosphatidylethanolamine (PE) and choline in Hcy metabolism, hypolipoproteinemia, liver function, and CVD [3, 7]. Several studies relating HHcy to disturbed HDL-C metabolism showed that Hcy can reduce circulating HDL-C via inhibiting ApoA-I protein synthesis and enhance HDL-C clearance [8, 9]. However, there are limited epidemic data about the relationship between HHcy and lipid profiles, especially in hypertensive patients.

Epidemiological studies demonstrated similar distributions of HHcy and hypertension, and both were related to an increased risk of cardiovascular events [10], [11]. In a large epidemiological study (NHANES III) [12], each 5 μmol/L increase in plasma Hcy levels was associated with an increase in systolic (SBP) and diastolic blood pressure (DBP) of 0.7 and 0.5 mmHg, respectively, in men, and 1.2 and 0.7 mmHg, respectively,

in women. However, the effect of Hcy-lowering interventions seemed to be paradoxical in the hypertensive population. Nutritional supplements could lower Hcy levels in most studies, but this was not always related to blood pressure [13], [14]. These results identified the need for prospective studies to illustrate whether there is direct association between Hcy and hypertension, or if these two factors just loosely coexist.

AIM OF THE STUDY: This study aims to investigate the association of plasma Hcy level with lipid profiles in hypertensive patients. We also tried to find out the risk of HHcy associated with hyperlipedemia. Further the role of BMI, smoking, diet and glycemic status in HHcy were also evaluated.

II. Materials And Methods:

The study was conducted in Hi-tech Medical College and Hospital, Rourkela and Kalinga Institute of Medical Sciences, Bhubaneswar after prior approval of the Institutional Ethics Committee. 148 hypertensive patients were identified and selected according to American Cardiology Association and American Heart Association guidelines on hypertension. (Table 1) All individuals were asked to sign the informed consent form after registration. Height, weight, and waist circumference were measured, and BMI was calculated for all of them. Pulse and BP were measured by manual sphygmomanometer in sitting position.

Fasting plasma glucose and serum lipid profile (cholesterol, TG, HDL) were estimated immediately after in automated analyzer (Erba Manheim EM 200) and HbA1c in D10 hemato analyzer. The LDL was calculated by Friedewald's method.

Plasma Hcy was measured using an auto analyzer (Erba Manheim EM 200) with the enzymatic method. This method mainly uses the S-adenosylhomocysteine (SAH) hydrolase reaction principle, in which SAH is hydrolyzed by hydrolytic enzymes into adenosine and Hcy, adenosine is immediately hydrolyzed into ammonia and hypoxanthine, nicotinamide adenine dinucleotide (NADH) is converted to NAD with ammonia and glutamic dehydrogenase, and the concentration of Hcy in the sample is proportional to the NADH transformation rate.

Desirable ranges for the variables measured were as per Atherosclerotic Cardiovascular Disease Risk Categories given in Table 4. [15]

Statistical analysis was performed using Graph Pad Prism. Causal relationship between the variables was determined by chi-square ($\chi 2$) test. The OR with 95% confidence interval (CI) was estimated using logistic regression predicting the factors associated with diabetes. For two-tailed p-values of <0.05 were considered significant, with 95% CIs.

III. Results:

The data analysis revealed that 31.48% (n = 51) of the participants were young adults of age group less than 40 years. The frequency of HHcy was calculated to be 65.4% (106/163) in this study group (Table 3). The incidence of moderate HHcy and intermediate HHcy was observed to be respectively, 37 (n =60) and 28.4% (n = 46). No patient in the study group had severe HHcy.

The mean age of participants was 47.4 ± 11.1 years. Frequency of hypertension was 40.82%. 62.96% had greater waist circumference, and 70.37% recorded high BMI, of which 25.93% (n = 42/162) were obese. Smoking history was positive in 37.65% cases and the diet of 60.49% study subjects were found to be mixed. Dyslipidemia was represented in 57.5% and hyperglycemia in 40.74 of the study subjects respectively.

The $\chi 2$ test in Table 5 revealed that age blood pressure, BMI, waist circumference, diet, smoking, exercise and glycemic status have a significant ($p < 0.05$) difference in proportion within each group.

As shown in Table 6, associated hypertriglyceridemia (TG ≥ 150 mg/dL) raises the risk 4.8 ($p < 0.05$) times for diabetes against the desirable level of TG. Individuals with elevated HDL (< 50 mg/dL) are at a 2.19 times more risk for HHcys in comparison with those with normal levels ($p < 0.05$).

Pearson correlation analysis demonstrated significant positive correlation between serum homocysteine levels with age, BMI, BP, waist circumference, plasma glucose, triglyceride (TG), high density lipoprotein (HDL) and very low-density lipoprotein (VLDL) as tabulated in Table 7.

Table 1: New ACC/AHA High Blood Pressure Guidelines.

Normal	Less than 120/80 mm Hg
Elevated	Systolic between 120-129 *and* diastolic less than 80
Stage 1	Systolic between 130-139 *or* diastolic between 80-89
Stage 2	Systolic at least 140 *or* diastolic at least 90 mm Hg
Hypertensive crisis	Systolic over 180 and/or diastolic over 120, with patients needing prompt changes in medication if there are no other indications of problems, or immediate hospitalization if there are signs of organ damage

Table 2: Classification of hyperhomocysteinemia.

Category	Levels in µmol/L
Normal	4-15
Moderate	>15-30
Intermediate	>30-100
Severe	>100

Table 3: Frequency of hyperhomocysteinemia in study group

Dependent variables	**Frequency**	**Percentage**
Normal Hcy	56/162	34.6
Moderate HHcy	60/162	37.0
Intermediate HHcy	46/162	28.4
Severe HHcy	0/162	----

Table 4: Desirable range for the measured variables

Variables	Desirable range
Waist circumference	Men: <94 cm; Women: <80 cm
BMI	18.5–24.9 kg/m2
Pulse	60-90 bpm
BP	<120/80
FPG	<100 mg/dl
Serum cholesterol	<200 mg/dl
Serum TG	<150 mg/dl
Serum LDL	<130 mg/dl
Serum HDL	>50 mg/dl
Serum VLDL	<30 mg/dl

Table 5: Percentage distribution of homocysteinemia status by physiological characteristics by chi-squared test.

Variable	**Normal Hcy**	**Mod HHcy**	**Inter HHcy**	Total	p-value
Age group in years					
20-40	18	21	12	51	
>40	38	39	34	111	0.614
Gender					
Males	30	32	28	90	
Females	26	28	18	72	0.735
BP (mm Hg)					
Elevated	38	24	8	70	
Stage 1	14	24	18	56	
Stage 2	4	12	20	36	<0.001*
BMI (kg/m^2)					
Normal (18.5–24.9)	36	10	2	48	
Overweight (25–29.9)	18	30	24	72	
Obese (≥30)	2	20	20	42	<0.001*
Waist circumference (cm)					
Normal	29	19	12	60	
High	27	41	34	102	0.016*
Diet					
Vegetarian	6	30	28	64	
Mixed	50	30	18	98	<0.001*
Smoking history					
Positive	35	10	16	61	
Negative	21	50	30	101	<0.001*
Exercise					
Yes	40	22	8	70	
No	16	38	38	92	<0.001*
Glycemic status					
Non diab	50	40	6	96	
Prediab	4	8	28	40	
Diabetics	2	12	12	26	<0.001*

*p < 0.05 significant difference

Table 6: Lipid profile association with hyperhomocysteinemia

Variables	Odds ratio	95% CI Lower	95% CI Higher	p-value
Total cholesterol (mg/dl) Desirable (<200) Moderate and high risk (≥200)	1..09	0.60	2.00	0.77
TG (mg/dl) Desirable (<150) Moderate and high risk (≥150)	4.80	2.65	8.69	<0.01**
HDL (mg/dl) Desirable (≥50) Moderate and high risk (<50)	2.19	1.33	3.62	<0.01*
LDL (mg/dl) Desirable (<129) Moderate and high risk (≥129)	1.31	0.70	2.46	0.39
VLDL (mg/dl) Desirable (<30) Moderate and high risk (≥30)	4.27	2.38	7.64	<0.01**

(Logistic regression, *p < 0.05 significant difference)

Table 7: Pearson correlation between serum homocysteine and physiological and biochemical parameters

Plasma glucose	Pearson correlation	Significance (two tailed)	N
Age	0.12	0.128	162
Pulse	0.11	0.164	162
BP	0.23	0.003*	162
BMI	0.21	0.007*	162
Waist circumference	0.18	0.022*	162
Plasma glucose	0.20	0.011*	162
Cholesterol	0.14	0.076	162
TG	0.29	0.0002*	162
LDL	0.15	0.057	162
HDL	0.22	0.005*	162
VLDL	0.30	0.0001*	162

*p < 0.05 significant difference

IV. Discussions:

Different studies examining the association between HHcy and lipid profiles in humans have had mixed conclusions, the most consistent findings indicate that higher Hcy is associated with decreased serum HDL-C and increased TG, which are consistent with the results of the present study. Our also included many additional covariates such as FBG, BMI, waist circumference, physical activity, among others which showed strong association with serum homocysteine levels.

The relationship between HHcy and hypertension has been proposed by multiple researchers, most of whom only used brachial BP as the BP parameter. The results of the present study are consistent with some of the results from prior studies.

A study has shown that cigarette smoking increases homocysteine, which is strongly correlated with cotininuria and plasma thiocyanates. Moreover, smokers had tendency to develop hypofolatemia and hypovitamin B12, particularly when the duration of consumption exceeded 20 years [16] which is consistent with this study.

We also found a strong association between diet and HHcy where subjects on mixed diet had fewer incidences of HHcy than subjects on vegetarian diet. This may be due to the fact that vitamin B12 levels are lower in vegetarians.

V. Conclusion:

Although not clearly applicable in all settings, it appears that there may be certain populations in whom the interactions of other multiple factors, such as BMI, waist circumference, smoking, diet, lipid status, and glycemic status, result in a heightened association between homocysteine levels and hypertension. Identifying the populations that may demonstrate this heightened association may benefit from the therapeutic reduction of homocysteine levels. Given the increasing disease burden of hypertension, continued efforts must be made to identify nontraditional risk factors associated with the development of hypertension. Once identified, innovative and targeted treatments of these nontraditional risk factors can be developed.

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