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Original Article

Is homocysteine an independent predictor of hypertension? A case-control study in an elderly population

Xiuqin Hong[1,3], Paul Ward[2], Richard J Woodman[2], Shuiyuan Xiao[1], Jian Chen[3], Na Zhang[3]

[1]*School of Public Health, Central South University, Changsha 410078, China;* [2]*School of Public Health, Flinders University, Adelaide 5001, Australia;* [3]*Institute of Gerontology, Hunan Geriatric Hospital, Changsha 410016, China*

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Abstract: Patients with hypertension and elevated homocysteine levels have a higher prevalence of risk factors for cardiovascular diseases (CVD) than individuals without either hypertension or elevated homocysteine levels, but the independence of homocysteine as a predictor of hypertension and vice-versa is controversial. This study was to explore the independence of hypertension and homocysteine (HCY) associations using a case-control study design based on a hospital in China. A case-control study was performed using 230 randomly selected 65-year-old and older inpatients with hypertension (cases) and 230 age and sex matched non-hypertensive controls. All participants were assessed for fasting triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), blood urea nitrogen (BUN), creatinine (CR), uric acid (UA), C-reactive protein (CRP), fasting glucose (BS), aspartate aminotransferase (AST) and body mass index (BMI). Data analysis was performed using conditional logistic regression. Compared to patients with hypertension, HCY, TG, TC, HDL, LDL, BUN, UA, CRP, BS and BMI were worse than controls. In multivariate analysis HCY (OR=1.22, P<0.001), BUN (OR=1.25, P=0.03) and CRP (OR=1.25, P=0.02) were independent predictors of hypertension. Amongst all subjects (cases and controls), the presence of elevated homocysteine was independently associated with hypertension (OR=9.93, P<0.001), TG (OR=3.56, P<0.001), LDL (OR=1.64, P=0.01), CRP (OR=1.50, P<0.001), BS (OR=0.75, P=0.02) and BMI (OR=1.14, P=0.001). Elevated homocysteine and hypertension are each independent predictors of each other. Hypertension is also independently associated with BUN and CRP, while elevated homocysteine is independently associated with TG, TC, LDL, CRP, BS and BMI.

Keywords: Homocysteine, hypertension, lipids, CRP, blood urea nitrogen, creatinine

Introduction

Hypertension is a serious public health concern as it is a major risk factor for other chronic diseases [1]. Homocysteine is a sulphur-containing non-protein amino acid that is formed during the metabolism of the essential amino acid methionine [3]. Elevated plasma homocysteine levels are recognized as an independent risk factor for various vascular diseases, such as atherosclerosis, cardiac hypertrophy, heart failure, and stroke particularly in the elderly [4]. The prevalence of cardiovascular disease and cerebrovascular disease in patients with hypertension and elevated homocysteine levels is much higher than that in patients without hypertension or elevated homocysteine levels [2]. A putative mechanism by which elevated homocysteine levels may cause vascular disease is through its potential to increase blood pressure [5] and the development of hypertension. As such, this may provide a potential mechanism linking elevated homocysteine with vascular disease [6, 7]. Although many studies have investigated the relationship between homocysteine and hypertension, results have so far been inconclusive. Some cross-sectional studies suggest a strong association between homocysteine and hypertension [8-10], while others have observed a positive but non-significant association [11-13]. The original Framingham Heart Study cohort and the Framingham Offspring cohort study also found no association between homocysteine and blood pressure [14, 15]. In addition, some studies have reported an inverse correlation

between homocysteine and the concentration of high density lipoproteins (HDLs). Homocysteine can reduce the concentration of HDL by inhibiting the hepatic synthesis of apolipoprotein A-I [1, 16]. Homocysteine may therefore contribute to vascular diseases via its effects on both blood pressure and HDL.

The contradictory evidence in relation to the association between homocysteine and BP may therefore in part be due to inadequate adjustment for known confounders including age, gender, race, diabetes, renal function and in particular HDL and other lipids. The aim of the present study was to more clearly determine the independent association between hypertension and homocysteine in elderly subjects without known diabetes or chronic renal disease using a case-control study design and adjusting for a wide variety of variables including lipids that might either mediate or confound the association between homocysteine and hypertension and vice versa.

Methods

Ethical approval

The ethics committee of Hunan Geriatric Hospital approved this study (2011GH0003).

Study population

Participants were selected from a total of 2231 patients with hypertension aged 65 and older attending a geriatric hospital between January 1, 2012 and December 31, 2012. We randomly selected 230 cases of patients with hypertension (defined as SBP≥140 mmHg or DBP≥90 mmHg or taking antihypertensive medication, according to the WHO/ISH (1999) criteria for hypertension), 122 men and 108 women; and aged 65 to 100 years old. For each case, one control subject was selected among older outpatients (age ≥65 years) attending a health examination at the Examination Center of the Geriatric Hospital. The controls were matched on age (±5 years), sex, and ethnicity. Control subjects were not taking antihypertensive drugs and all had a blood pressure less than 140/90 mmHg. All subjects resided in the Hunan province region of China. Both cases and controls were excluded on the basis of chronic renal diseases, known diabetes, vitamin-B and folic acid therapy and the use of lipid-lowering drugs, all of which might influence lipid concentrations as well as both hypertension and homocysteine. The baseline characteristics of the cases and controls were similar, highlighting their comparability. Written informed consent was obtained from all participants of the study. The study protocol was approved by the Geriatric Hospital Ethics Committee.

Measurements

All subjects provided information on sociodemographic characteristics and self-reported histories of diabetes, chronic renal diseases and whether or not they were taking vitamin-B, folic acid and lipid-lowering drugs. Weights and heights of all study subjects were measured by registered nurses to calculate body mass index (BMI). The blood pressure of all study subjects was measured three times by medical doctors one minute apart and with the subject resting comfortably, back supported in sitting position after a 10-15 minutes relaxation period. The average of three blood pressure values was taken to represent the blood pressure used for analysis. A mercury sphygmomanometer was used for all measurement with a medium- or a large-sized cuff, according to the subject's arm circumference.

An overnight fasting blood sample was collected by registered nurses. All blood was centrifuged within minutes of collection and the plasma was stored at -80°C for later biochemical measurement of the concentration of homocysteine (HCY), lipid profile, blood urea nitrogen (BUN), creatinine (CR), C-reactive protein (CRP), fasting glucose (BS), aspartate aminotransferase (AST) and uric acid (UA) by the Laboratory of Geriatric Hospital (grade A tertiary hospital, Hunan region Geriatric Hospital of China). Total plasma homocysteine levels were measured using the homocysteine microplate enzyme immunoassay assay (cut-off point: 15 μmol/L). TG, TC, HDL, BUN and UA were assayed using colorimetric methods. CR was calculated using the Cockroft-Gault equation. LDL was quantified by gas chromatography. (AST) was measured with an immunological method. The normal reference ranges were considered as BUN: 2.5-7.2 mmol/L, BS: 3.89-6.11 mmol/L, TG: 0.45-1.69 mmol/L, TC: 3.4-5.2 mmol/L, HDL: 0.78-1.81 mmol/L, LDL: 1.68-3.56 mmol/L, UA: 150-440 μmmol/L, Cr; women 70-106 and men 70-116 μmmol/L.

Table 1. Comparison of clinical and biochemical indices in non-hypertensive and hypertensive subjects

	Non-hypertensive (n=230) Mean ± SD	Hypertensive (n=230) Mean ± SD	*p*-value
Age (yrs)	75.6±6.8	75.7±6.8	0.96
Gender (M/F)	137/93	137/93	1.00
BMI (kg/m^2)	26.5±3.4	28.4±3.5	<0.001
SBP (mmHg)	118.4±11.7	141.4±17.1	<0.001
DBP (mmHg)	70.0±11.4	87.8±10.6	<0.001
FG (mmol/L)	5.18±0.94	5.53±1.27	<0.001
FG7.0 mmol/l or above, n (%)	12 (5.2)	15 (6.5)	0.55
TG (mmoL/L)	1.41±0.65	1.81±0.82	<0.001
TC (mmoL/L)	4.34±0.78	4.54±0.85	0.007
HDL (mmoL/L)	1.26±0.32	1.19±0.29	0.009
LDL (mmoL/L)	2.49±0.63	2.67±0.81	0.01
BUN (mmoL/L)	5.50±1.41	6.64±2.16	<0.001
CR (μmoL/L)	87.0±25.7	90.4±39.9	0.26
UA (μmoL/L)	321.8±81.7	344.7±89.6	0.005
CRP (mg/L)	4.59±1.59	5.95±1.61	<0.001
AST (μ/g)	18.8±9.1	20.8±14.3	0.07
HCY (μmoL/L)	8.49±5.20	15.80±4.78	<0.001

HCY: homocysteine, TG: triglycerides, TC: total cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein. BUN: blood urea nitrogen, CR: creatinine, UA: uric acid, CRP: C-reactive protein, FG: fasting glucose, AST: aspartate aminotransferase, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Statistical analysis

All analyses were performed using STATA statistical software version 12.0 (STATACorp, Texas, USA). Baseline characteristics of the subjects were compared using a paired t-test. The association between hypertension and patients clinical characteristics and biochemistry were assessed using univariate and multivariate conditional logistic regression. Stepwise logistic regression was used to assess the independent predictors of hypertension. Additional adjustment for BMI and age was also performed. Univariate associations between homocysteine and clinical characteristics were assessed separately for patients with hypertension and controls using the Spearman rho correlation coefficient. The association between the presence of high homocysteine and the presence of hypertension and other clinical characteristics was assessed using binary logistic regression. Stepwise regression was used to build a parsimonious model consisting of independent predictors and then an additional adjustment for age was also performed. Regression coefficients were considered as being statistically significant with a Type 1 error rate of P<0.05.

Results

Clinical features of patients with and without hypertension

Table 1 compares the laboratory parameters and clinical characteristics in the two groups. Plasma homocysteine was significantly higher in patients with hypertension compared to their age and sex matched controls (P<0.001). The lipid profile (triglycerides, total cholesterol, low density lipoprotein and high density lipoprotein) was more favorable amongst the control group, and blood urea nitrogen (BUN), uric acid (UA), C-reactive protein (CRP), fasting glucose (BS) and body mass index (BMI) was also more favorable amongst controls. However, creatinine (CR) and aspartate aminotransferase (AST) was not different between the two groups.

Parameters associated with hypertension

Table 2 displays the results of the univariate and multivariate conditional logistic regression. In univariate analysis, HCY, TG, TC, LDL, BUN, UA, CRP, BS, SBP, DBP and BMI were positively associated with the odds of hypertension while high density lipoprotein was inversely associated. In multivariate analysis, HCY (OR=1.23, 95% CI 1.16 to 1.31; P<0.001), BUN (OR=1.24, 95% CI 1.02 to 1.51; P=0.031) and CRP (OR=1.25, 95% CI 1.04 to 1.51; P=0.02) were positively and independently associated with the odds of hypertension. These associations remained after additionally adjusting for age and BMI (Model 2) (**Table 2**).

The association between homocysteine and the clinical and biochemical indicators amongst non-hypertension and hypertension are presented in **Table 3**. **Table 4** displays the results of the univariate and multivariate conditional logistic regression which parameters associated with high homocysteine. In univariate analysis, HCY was positively associated with TG, TC,

Table 2. Unadjusted and adjusted odds ratios for association between risk factors and presence of hypertension[1]

	Univariate analysis		Multivariate analysis Model 1		Multivariate analysis Model 2	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
HCY	1.28 (1.20, 1.35)	<0.001	1.23 (1.16, 1.31)	<0.001	1.22 (1.14, 1.30)	<0.001
TG	2.29 (1.68, 3.11)	<0.001				
TC	1.37 (1.08, 1.74)	0.008				
HDL	0.43 (0.22, 0.83)	0.012				
LDL	1.39 (1.07, 1.80)	0.013				
BUN	1.51 (1.31, 1.75)	<0.001	1.24 (1.02, 1.51)	0.031	1.24 (1.02, 1.51)	0.03
CR	1.00 (0.998, 1.009)	0.26				
UA	1.003 (1.001, 1.005)	0.006				
CRP	1.75 (1.49, 2.05)	<0.001	1.25 (1.04, 1.51)	0.02	1.25 (1.04, 1.51)	0.02
BS	1.41 (1.15, 1.73)	0.001				
AST	1.02 (0.998, 1.032)	0.08				
SBP	1.12 (1.09, 1.15)	<0.001				
DBP	1.17 (1.13, 1.22)	<0.001				
BMI	1.21 (1.13, 1.30)	<0.001				

[1]Estimated using conditional logistic regression. Model 1: Using stepwise regression and adjusted for each variable listed. Model 2: Additionally adjusted for age and BMI.

Table 3. Spearman rho correlation coefficients with homocysteine amongst controls and cases

	Controls		Cases	
	Rho	*p*-value	Rho	*p*-value
TG	0.42	<0.001	0.32	<0.001
TC	0.28	<0.001	0.18	0.006
HDL	-0.10	0.13	-0.21	0.002
LDL	0.18	0.005	0.30	<0.001
BUN	0.13	0.05	0.25	<0.001
CR	0.03	0.63	0.10	0.11
UA	0.14	0.03	0.07	0.29
CRP	0.27	<0.001	0.33	<0.001
BS	0.04	0.51	0.04	0.55
AST	-0.012	0.85	0.05	0.46
SBP	0.04	0.53	0.43	<0.001
DBP	0.03	0.63	0.25	<0.001
BMI	0.26	<0.001	0.55	<0.001

TG: triglycerides, TC: total cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, BUN: blood urea nitrogen, CR: creatinine, UA: uric acid, CRP: C-reactive protein, BS: fasting glucose, AST: aspartate aminotransferase, SBP: systolic blood pressure, DBP: diastolic blood pressure.

LDL, BUN, UA, CRP, and BMI in the non-hypertensive group and with TG, TC, LDL, BUN, CRP, SBP, DBP, and BMI in the hypertensive group. In addition, homocysteine was inversely associated with HDL in the hypertensive group. In the multivariate logistic regression analysis of all subjects, hypertension and triglycerides (TG) as well as LDL, BS, CRP and BMI were all significantly and independently associated with the odds of elevated HCY. Although HDL was inversely associated with homocysteine in univariate analysis it was not independently associated with high homocysteine. Model 2 results were similar to that for Model 1 (**Table 4**).

Discussion

Our study has contributed to evidence suggesting that in elderly subjects the presence of hypertension is strongly and independently associated with homocysteine and also that the presence of hypertension is independently associated with elevated homocysteine. Hypertension was also independently associated with BUN and CRP but not with other lipids or inflammatory markers. Plasma concentrations of TG, LDL, CRP and BS, and BMI showed the strongest associations with elevated homocysteine levels.

An independent relationship between homocysteine and aortic augmentation index has been reported amongst patients with essential hypertension and isolated office hypertension, but not amongst normotensives [10]. The increased risk of atherosclerosic disease including coronary artery disease and cardio-

Table 4. Unadjusted and adjusted odds ratios for association between risk factors and presence of high homocysteine[1]

	Univariate analysis		Multivariate analysis Model 1		Multivariate analysis Model 2	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Hypertension (Yes versus No)	14.0 (8.9, 22.1)	<0.001	9.58 (5.56, 16.52)	<0.001	9.93 (5.72, 17.2)	<0.001
TG (mmol/l)	5.34 (3.61, 7.92)	<0.001	3.48 (2.18, 5.56)	<0.001	3.56 (2.21, 5.72)	<0.001
TC	1.90 (1.48, 2.45)	<0.001				
HDL	0.27 (0.14, 0.53)	<0.001				
LDL	1.98 (1.50. 2.61)	<0.001	1.65 (1.12, 2.43)	0.01	1.64 (1.11, 2.42)	0.01
BUN	1.40 (1.24, 1.59)	<0.001				
CR	1.003 (0.998, 1.009)	0.22				
UA	1.004 (1.002, 1.006)	<0.001				
CRP	1.93 (1.67, 2.24)	<0.001	1.48 (1.22, 1.78)	<0.001	1.50 (1.24, 1.81)	<0.001
BS	1.24 (1.04, 1.48)	0.02	0.75 (0.59, 0.95)	0.02	0.75 (0.59, 0.96)	0.02
AST	1.02 (1.002, 1.039)	0.03				
SBP	1.05 (1.04, 1.07)	<0.001				
DBP	1.08 (1.06, 1.10)	<0.001				
BMI	1.24 (1.17, 1.32)	<0.001	1.15 (1.06, 1.24)	<0.001	1.14 (1.06, 1.24)	0.001

[1]Estimated using binary logistic regression. Model 1: Using stepwise regression and adjusted for each variable listed. Model 2: Additionally adjusted for age and BMI.

vascular disease due to hypertension has been attributed to various potential mechanisms including vascular oxidative stress, endothelial dysfunction as well as cellular injury caused by elevated homocysteine levels [17-19] which is supported by results from the present study.

Although our study demonstrated that elevated homocysteine levels were associated with plasma lipids (TG, TC, HDL, LDL) in this elderly population, lipid profiles were not independently associated with hypertension. However, given that TG and LDL are putative independent risk factors for elevated homocysteine levels, homocysteine might help mediate the effects of lipids on hypertension. Homocysteine might additionally increase the risk of cardiovascular disease amongst patients with both hypertension and high homocysteine by reducing the concentration of HDL [20]. In addition, oxidative modification of low density lipoprotein has been suggested to explain the role of homocysteine in the pathogenesis of vascular disease [21]. Plasma lipoproteins are also susceptible to homocysteinylation [22, 23].

Both elevated homocysteine levels and hypertension were associated with BUN and CRP. These biochemical indices have both been proposed as causal factors of hypertension although not of elevated homocysteine. Since BUN is excreted by glomerular filtration, our findings provide a logical interpretation for the relationship between hypertension and BUN [24]. In addition BUN and C-reactive protein (CRP) have both been linked to oxidative stress [25]. Uric acid is an important plasma antioxidant which can help to maintain nitric oxide levels and endothelial function [26, 27] whereas homocysteine may cause endothelial damage and LDL oxidation [28]. Reducing oxidative stress and inflammation is likely to be beneficial for hypertension [29]. Together these results support the strong interplay between homocysteine, lipids, renal function, inflammation and oxidative stress. Although uric acid was associated with both hypertension and high Homocysteine in univariate analysis, it was not independently associated with either. These results support other studies that suggest uric acid is more likely to be associated with renal disease [30-32] than with hypertension. The Framingham Heart Study also reported that uric acid was not a causal risk factor for cardiovascular disease and was not an independent predictor of hypertension [33]. The increase of uric acid in hypertension is thought to be due to the decrease in renal blood flow that accompanies the hypertensive state which stimulates urate reabsorption [34].

Our study had several limitations. First, the observational case-control design does not allow the direction of causality to be determined. Second, our study fails to consider other confounders that may have contributed to hypertension, Homocysteine and oxidative stress including nutritional factors, genetics,

disease history, behavioral habits and lifestyle, working conditions, physical status and stress. Third, the hypertensive patients were receiving anti-hypertensive medication so that blood pressure values were not always a true indication of underlying blood pressure and the association with HCY may therefore be conservative. Although diabetes was an exclusion criterion for the study, approximately 5 percent of subjects in each group had fasting glucose levels greater than 7 mmol/l. The generalizability of our results may also be limited to our study population aged 65-years-old and older. In addition, the outpatients we studied as controls may not have been as representative a sample of the underlying population from where the cases came, as an inpatient population from within the same hospital in regards to factors such as mobility, lifestyle and diet, all of which may affect both blood pressure and homocysteine levels. However, any differences in socio-economic factors between an inpatient and outpatient control population are likely to have been small. Any follow-up cohort study should consider these and other potential sources of bias and confounding and include all members of the community in order to that our results can be generalized to a wider population.

Conclusion

Elevated homocysteine levels and hypertension have been proposed as causal risk factors for each other although findings have been inconsistent. We observed them to be strongly and independently associated with each other and BUN and CRP were also independently and positively associated with hypertension. Triglycerides, LDL, CRP, blood sugar and BMI were also strongly associated with elevated HCY. Together with the established literature the results help clarify the potential mechanisms and interactions that exist between elevated homocysteine concentrations and other biomarkers that influence hypertension via increased inflammation and oxidative stress.

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Disclosure of conflict of interest

None.

Address correspondence to: Shuiyuan Xiao, School of Public Health, Central South University, Changsha 410078, Hunan, China. Tel: 86-1390749-4509; Fax: 86-731-84805454; E-mail: ShuiyuanXiaocn@126.com

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