

Factors associated with hyperhomocysteinemia in relatively healthy Taiwanese adults

A retrospective medical record study

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Abstract

Elevated homocysteine levels have been proposed as a risk factor for cardiovascular disease. The aim of this study was to evaluate factors associated with hyperhomocysteinemia in relatively healthy Taiwanese adults.

A retrospective cross-sectional study was conducted using data from the health examination database in a medical center located in southern Taiwan. Hyperhomocysteinemia was defined as a plasma homocysteinemia level $>15 \mu\text{mol/L}$. Factors associated with hyperhomocysteinemia were evaluated using univariate and multiple stepwise logistic regression analyses.

A total of 817 adults with a mean age of 55.5 years were included in the present study, and of them, 67 (8.2%) had hyperhomocysteinemia. Results from multiple logistic regression analysis showed that male sex (Odd ratio [OR] = 12.28, 95% CI = 2.94–51.27, $P = .001$), advanced age (OR = 1.37 per 10 years, 95% CI = 1.06–1.77, $P = .017$), triglycerides (OR = 1.02 per 10 mg/dL, 95% CI = 1.01–1.04, $P = .010$), and uric acid (OR = 1.27, 95% CI = 1.09–1.49, $P = .004$) were significantly and independently associated with hyperhomocysteinemia.

In this retrospective medical record study, male sex, advanced age, higher plasma level of triglyceride, and uric acid were significantly associated with hyperhomocysteinemia in relatively healthy Taiwanese adults.

Abbreviations: BMI = body mass index, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rates, hs-CRP = high-sensitivity C-reactive protein, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, MetS = metabolic syndrome, SBP = systolic blood pressure, SREBP = sterol regulatory element-binding protein.

Keywords: homocysteine, metabolic factors, uric acid, metabolic syndrome

1. Introduction

Cardiovascular disease is one of the most common leading causes of mortality and morbidity globally. Well-established risk factors for cardiovascular disease include hypertension, dyslipidemia, diabetes mellitus, and obesity. Recent research suggested that hyperhomocysteinemia is an independent predictor for ischemic heart disease and stroke in healthy population.^[1,2] In addition, its

values in the prediction of short-term outcome in patients diagnosed of ischemic stroke^[3] and of major adverse cardiac events in patients with history of acute coronary syndrome^[4] have been reported. There is also evidence linking elevated homocysteine levels with vascular dementia,^[5] Alzheimer's disease,^[6] bone fractures,^[7] and diabetic kidney disease.^[8]

Homocysteine is a naturally occurring amino acid involving in a number of key metabolic processes, including the methylation and sulphuration pathways. Blood levels of homocysteine are affected by various dietary factors, including folic acid and vitamin B12, pregnancy, and by various disorders such as renal impairment and genetic defects.^[9,10] Homocysteine could exert adverse effects on endothelium and smooth muscle cells, resulting in endothelial dysfunction, vascular smooth muscle cell proliferation, oxidative stress, increased collagen synthesis, and arterial stiffness.^[11]

While there are numerous studies investigating the role of hyperhomocysteinemia as a risk factor for cardiovascular disorders, relatively little research has been focused on factors associated with hyperhomocysteinemia,^[12,13] particularly in healthy population. Therefore, the aim of this study was to investigate factors associated with hyperhomocysteinemia in relatively healthy Taiwanese adults.

2. Methods

2.1. Subjects

In this retrospective cross-sectional study, data from the health examination database in a medical center located in southern

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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Taiwan between January 2016 and December 2016 were extracted. A total of 4858 adults had undergone health examination during this period of time. Individuals with missing anthropometric or biochemical measurements were excluded, leaving 817 patients retained in the present study. The research was approved by the Chang Gung Medical Foundation Institutional Review Board (No. 201900130B0).

Information including sex, age, height, weight, waist circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were obtained by trained nurses. Body mass index (BMI) was calculated by using the formula as weight in kilograms divided by the height in meters squared. Blood samples were collected for measuring fasting plasma glucose, uric acid, high-sensitivity C-reactive protein (hs-CRP), homocysteine, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

2.2. Definition of hyperhomocysteinemia and metabolic syndrome

Hyperhomocysteinemia was defined as a plasma level of homocysteine $>15 \mu\text{mol/L}$.^[9] The definition of metabolic syndrome (MetS) was adopted from the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATP III).^[10] Subjects were diagnosed with MetS when they met any three or more of the following five components:

1. abdominal obesity (waist circumference $>90 \text{ cm}$ in men or $>80 \text{ cm}$ in women, the recommended criteria for Asian Americans),
2. high fasting blood glucose level ($\geq 100 \text{ mg/dL}$),
3. high triglyceride level ($\geq 150 \text{ mg/dL}$),
4. high SBP ($\geq 130 \text{ mmHg}$) or DBP ($\geq 85 \text{ mmHg}$),
5. low HDL-C level ($\leq 40 \text{ mg/dL}$ in men or $\leq 50 \text{ mg/dL}$ in women).

2.3. Statistical analysis

The data were expressed as mean and standard deviation for continuous variables and frequency with percentage for categorical variables. The χ^2 -test was used for comparing categorical variables and the Mann-Whitney *U* test was used for the comparison of continuous variables. Univariate and multiple logistic regression analyses were conducted to investigate factors associated with hyperhomocysteinemia. The backward maximum likelihood ratio test was used for selecting independent and significant factors associated with hyperhomocysteinemia. A *P* value $<.05$ was considered as statistically significant. The SPSS software version 22.0 (IBM Corp, Armonk, NY) was used for all analysis.

3. Results

The baseline characteristics of the study participants are presented in Table 1. The mean age of 817 participants was 55.5 years (standard deviation [SD] 10.8 years). There were 264 females (32.3%) and 553 males (67.7%). The mean plasma homocysteine level was $10.36 \text{ (SD } 3.58) \mu\text{mol/L}$.

When participants were categorized into hyperhomocysteinemia ($n=67$) and normal homocysteine level ($n=750$), several differences in anthropometric or biochemical measurements were observed (Table 1). The proportion of male participants with hyperhomocysteinemia was significantly higher than that of females ($P < .001$). Age ($P = .033$), waist circumference ($P = .002$), triglycerides ($P = .006$), SBP ($P = .003$), DBP ($P = .001$), fasting blood glucose ($P = .039$), TC/HDL-C ratio ($P = .034$), and uric acid ($P < .001$) were significantly higher in the hyperhomocysteinemia group. Conversely, HDL-C ($P = .009$) were significantly lower in the hyperhomocysteinemia group. In addition, the proportion of participants with metabolic syndrome was significantly higher in hyperhomocysteinemia group ($P < .001$).

Table 1
Baseline characteristics of the study population (N=817).

Variable	n (%) or mean \pm standard deviation			P
	Total N=817 (100)	Hyper-homocysteinemia n=67 (8.2%)	Normal homocysteine n=750 (91.8%)	
Sex				<.001
Female	264 (32.3)	2 (3.0)	262 (34.9)	
Male	553 (67.7)	65 (97.0)	488 (65.1)	
Age (years)	55.5 \pm 10.8	58.2 \pm 9.8	55.3 \pm 10.9	.033
Body mass index (kg/m ²)	25.2 \pm 3.8	25.8 \pm 3.7	25.1 \pm 3.8	.139
Waist circumference (cm)	84.7 \pm 10.8	88.8 \pm 10.3	84.4 \pm 10.7	.002
TC (mg/dL)	203.1 \pm 37.2	203.0 \pm 43.1	203.1 \pm 36.7	.781
HDL-C (mg/dL)	50.1 \pm 13.4	46.0 \pm 12.8	50.4 \pm 13.4	.009
Triglycerides (mg/dL)	136.8 \pm 100.3	182.3 \pm 183.0	132.7 \pm 88.4	.006
LDL-C (mg/dL)	123.3 \pm 32.8	122.3 \pm 38.0	123.4 \pm 32.3	.824
SBP (mmHg)	128.7 \pm 20.2	134.8 \pm 17.8	128.2 \pm 20.3	.003
DBP (mmHg)	85.0 \pm 11.6	89.8 \pm 12.3	84.6 \pm 11.5	.001
Fasting blood glucose (mg/dL)	104.7 \pm 25.4	111.5 \pm 31.5	104.0 \pm 24.7	.039
TC/HDL-C (mg/dL)	4.28 \pm 1.19	4.68 \pm 1.49	4.24 \pm 1.16	.034
LDL-C/HDL-C (mg/dL)	2.62 \pm 0.93	2.84 \pm 1.11	2.60 \pm 0.91	.079
Uric acid (mg/dL)	6.33 \pm 1.56	7.20 \pm 1.86	6.25 \pm 1.51	<.001
Plasma hs-CRP (mg/dL)	2.33 \pm 4.09	2.96 \pm 6.78	2.24 \pm 3.77	.182
Plasma homocysteine ($\mu\text{mol/L}$)	10.36 \pm 3.58	18.66 \pm 4.40	9.63 \pm 2.36	<.001
Metabolic syndrome, n (%)				<.001
Yes	237 (29.0)	32 (47.8)	205 (27.3)	
No	580 (71.0)	35 (52.2)	545 (72.7)	

DBP = diastolic blood pressure, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, SBP = systolic blood pressure, TC = total cholesterol.

Table 2
Univariate and multiple logistic regression analyses of hyperhomocysteinemia.

Variable	Univariate logistic regression		Multiple logistic regression	
	Odd ratio (95% confidence interval)	P	Adjusted odd ratio (95% confidence interval)	P
Sex				
Female	1.00		1.00	
Male	17.45 (4.24–71.83)	<.001	12.28 (2.94–51.27)	.001
Age (per 10 years)	1.29 (1.01–1.65)	.039	1.37 (1.06–1.77)	.017
Body mass index			–	–
Normal	1.00			
Underweight	1.04 (0.13–8.24)	.972		
Overweight	1.57 (0.85–2.91)	.153		
Obese	1.47 (0.79–2.73)	.229		
Waist circumference (cm)	1.04 (1.02–1.06)	.001	–	–
Total cholesterol (per 10 mg/dL)	1.00 (0.93–1.07)	.975	–	–
HDL-C (per 10 mg/dL)	0.75 (0.60–0.94)	.011	–	–
Triglyceride (per 10 mg/dL)	1.03 (1.01–1.05)	.001	1.02 (1.01–1.04)	.010
LDL-C (per 10 mg/dL)	0.99 (0.92–1.07)	.789	–	–
SBP (per 10 mg Hg)	1.16 (1.04–1.31)	.010	–	–
DBP (per 10 mg Hg)	1.43 (1.17–1.76)	.001	–	–
Fasting blood glucose (per 10 mg/dL)	1.10 (1.02–1.19)	.011	–	–
Uric acid (mg/dL)	1.42 (1.22–1.65)	<.001	1.27 (1.08–1.49)	.004
Hs-CRP (per 10 mg/dL)	1.35 (0.87–2.09)	.178	–	–
Metabolic syndrome	2.43 (1.47–4.03)	.001	–	–
No				
Yes				

BMI=body mass index, DBP=diastolic blood pressure, HDL=high-density lipoprotein, hs-CRP=high-sensitivity C-reactive protein, LDL=low-density lipoprotein, SBP=systolic blood pressure, TC=total cholesterol.

Results from the univariate and multiple logistic regression analyses are shown in Table 2. Univariate logistic regression analyses revealed that sex, age, waist circumference, HDL-C, triglycerides, SBP, DBP, fasting blood glucose, uric acid, and metabolic syndrome were significantly associated with hyperhomocysteinemia. In addition, multiple logistic regression analysis showed that being male (OR=12.28, $P=.001$), advanced age (OR=1.37, $P=.017$), high triglyceride (OR=1.02, $P=.010$), and high uric acid (OR=1.27, $P=.004$) remained independently and significantly associated with hyperhomocysteinemia.

4. Discussion

This retrospective cross-sectional study based on health examination records on relatively healthy adults revealed a number of factors were associated with hyperhomocysteinemia, including being male, advanced age, high triglyceride, high uric acid levels. The mean level of homocysteine found in the present study was comparable to that reported by a population-based study of 24,826 Taiwanese people.^[14]

In the present study, being male was significantly associated with hyperhomocysteinemia. The differences might be explained by a sex difference in the metabolism of homocysteine. A study in adults without cardiac risk factors showed a significant higher rate of remethylation, that is, the process of homocysteine remethylated back to methionine, in women than in men.^[15] Therefore, it was reasonable to expect that homocysteine level is higher in men than women. In addition, it has been suggested that creatine and the subsequent creatinine synthesis could be related to muscle mass, which might explain the higher homocysteine levels in men than women.^[16] Furthermore, hormonal differences between the sexes have also been proposed. A clinical study with

transsexuals showed that male-to-female subjects who were treated with ethinyl estradiol and antiandrogen had significantly decreased levels of homocysteine. Conversely, female-to-male transsexuals who underwent testosterone treatment had increased plasma homocysteine.^[17]

Advanced age was found to be significantly associated with hyperhomocysteinemia in this study. This finding is consistent with previous studies.^[18,19] The increase homocysteine levels in older people could be explained by the physiologically associated renal function decline. Previous research indicated that glomerular filtration rate could serve an important role in the clearance of homocysteine and creatinine.^[20] A study on Taiwanese adults also reported that plasma homocysteine level was inversely associated estimated glomerular filtration rates (eGFR).^[21]

The present study also found that plasma triglyceride level was significantly associated with hyperhomocysteinemia. A community-based study on 4660 Chinese adults reported that hyperhomocysteinemia was significantly associated with increasing risk of hypertriglyceridemia and low HDL-C, after adjusting confounders with a multiple logistic regression analysis.^[22] Experimental studies have suggested that homocysteinemia-related endoplasmic reticulum stress increases the expression of sterol regulatory element-binding proteins (SREBPs), which further promote cholesterol and triglyceride synthesis.^[23] The result was demonstrated in an animal study in which increased plasma triglyceride was observed in mice with elevated plasma homocysteine induced by a high methionine diet.^[24]

The plasma uric acid level was observed to be a significant and independent factor associated with hyperhomocysteinemia in this study. A cross-sectional population-based study on 5913 adults in Switzerland also found a positive and significant association between uric acid and homocysteine.^[25] In addition, a study on 133 patients with crystal proven gout showed that plasma urate

was one of the significant independent predictors of plasma homocysteine.^[26] Moreover, a large cross-sectional study of data from a screening center in Israel found a significant association between hyperhomocysteinemia and hyperuricemia, particularly in males. The authors suggested that the combined effect of these two conditions might accelerate the process of atherosclerosis^[27] through inducing reactive oxygen species and thereby impair endothelial function.^[28] The additive effect of hyperhomocysteinemia and hyperuricemia in the pathogenesis of vascular disease deserves further investigation.

There are several limitations associated with this study. First, measurements were obtained from medical records using a retrospective cross-sectional design, and hence a causal relationship could not be inferred. Second, medical records were obtained from a single medical center, which might not represent the general population in Taiwan. Third, information on lifestyle factors, such as chronic alcoholism, smoking, and dietary habits that could potentially affect homocysteine levels were not available in the medical records, and therefore, could not be adjusted with statistical models.

5. Conclusions

Hyperhomocysteinemia was found to be associated with male sex, advanced age, high triglycerides, and uric acid levels. Further prospective studies are warranted to evaluate the role of hyperhomocysteinemia together with hypertriglyceridemia and hyperuricemia in the prediction of cardiovascular and neurological disorders.

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