Hyperhomocysteinemia in association with male gender, advanced age, uric acid and metabolic syndrome: A retrospective cross-sectional study

Po-Ju Chen
Chang Gung Memorial Hospital Kaohsiung Branch
Yueh-Chien Lu
Chang Gung Memorial Hospital Kaohsiung Branch
Pei-Ming Wang
Chang Gung Memorial Hospital Kaohsiung Branch
Song-Seng Loke (loke@cgmh.org.tw)
Chang Gung Memorial Hospital Kaohsiung Branch https://orcid.org/0000-0003-1182-063X

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Abstract

Background Elevated homocysteine level has been proposed as a risk factor for cardiovascular disease. The aim of this study is to evaluate the connection between hyperhomocysteinemia with other factors for early detection of possible cardiovascular disease. Methods The data in this retrospectively designed cross-sectional study was retrieved from the health examination database in a medical center located in southern Taiwan in 2016. The correlation of hyperhomocysteinemia with sex, age, body mass index, waist circumference, lipid profile, blood pressure, uric acid, high sensitivity C-reactive protein and lipoprotein were investigated. Both simple and multiple stepwise logistic regression models were used for the assessment of their connection. Results A total of 878 subjects with mean age of 55.4 ± 10.8 years were included in the current study and 73 (9.1%) participants had elevated homocysteine levels. Simple logistic regression analysis showed elevated Hcy was significantly associated with sex (OR 0.11, 95% CI 0.04-0.31, P < 0.001), age (OR 1.03, 95% CI 1.00-1.05, P < 0.035), waist circumference (OR 1.04, 95% CI 1.02-1.06, P = 0.001), HDL-C (OR 0.97, CI 0.95-0.99, P = 0.011), triglyceride (OR 1.00, CI 1.00-1.01, P = 0.002), SBP (OR 1.02, CI 1.01-1.03, P = 0.004), DBP (OR 1.04, CI 1.02-1.06, P = 0.001), sugar level (OR 1.01, CI 1.00-1.02, P = 0.021), uric acid (OR 1.39, CI 1.20-1.60, P < 0.001) and the presence of metabolic syndrome (OR 1.81, CI 1.12-2.93, P = 0.016). Multiple stepwise logistic regression analysis was applied and the result showed that male gender (OR 0.15, 95% CI 0.05-0.43, P < 0.001), advanced age (OR 1.03, 95% CI 1.00-1.05, P < 0.036), triglycerides (OR 1.002, 95% CI 1.001-1.004, P = 0.022), systolic blood pressure (OR 1.02, 95% CI 1.00-1.03, P = 0.023) and uric acid (OR 1.26, 95% CI 1.07-1.47, P = 0.005) were significantly associated with the elevation of plasma homocysteine. Conclusions Several factors are associated with hyperhomocysteinemia in asymptomatic subjects including sex, age, uric acid and metabolic syndrome components. Among these factors, male, advanced age, systolic blood pressure, plasma level of triglyceride and uric acid were independently associated with hyperhomocysteinemia.

Background

Cardiovascular disease is one of the most common leading causes of mortality and morbidity globally. In Taiwan, cardiac disease was the second major cause of death following by malignant neoplasm in 2016. Well-established risk factors for cardiovascular disease include hypertension, dyslipidemia, diabetes mellitus and obesity. Homocysteine (Hcy), an amino acid produced during the metabolism of methionine, is considered as an independent factor for cardiovascular disease [1]. Previous studies concluded that Hcy exerts adverse effects on endothelium and smooth muscle cells [2], resulting in endothelial dysfunction, vascular smooth muscle cells proliferation, oxidative stress, increased collagen synthesis and arterial stiffness [2]. Besides Hcy, inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) are proposed as novel predictors for cardiovascular disease based on the concept that inflammation serves as a major role in the progression of atherothrombosis. The predictive role of hs-CRP for cardiovascular disease has been established by previous research [3]. Furthermore, oxidative stress is regarded as a contributor to cardiac and vascular abnormalities [4]. Xanthine oxidase, an enzyme participating in the uric acid synthesis, is suggested to be one of the sources of reactive oxygen species.

The upregulation of xanthine oxidase and consequent elevation of uric acid is considered as a potential biomarker for cardiovascular disease [5].

We conducted a cross-sectional study to investigate the association between hyperhomocysteinemia and other cardiovascular risk factors mentioned above. The aim of this article is to provide evidence for early identification of asymptomatic populations at high risk of cardiovascular disease with Hcy and other serum biomarkers.

Methods

Subjects

This retrospective, cross-sectional study was conducted by applying data from a health examination database in a medical center located in southern Taiwan from January 2016 to December 2016. A total of 4858 subjects had undergone health examinations during this period of time. Subjects who had missing anthropometric, metabolic factors, plasma hs-CRP, plasma lipoprotein or plasma Hcy data (n = 3980) were excluded, leaving 878 patients retained for the present study. The research was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No.201900130B0).

Information from the subjects including sex, age, height (cm), weight (kg), waist circumference (cm), 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, hs-CRP, lipoprotein, Hcy, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).

Definition of hyperhomocysteinemia and metabolic syndrome

The normal concentration of Hcy in this study was defined as ≤ 15 μmol/L and hyperhomocysteinemia was considered > 15 μmol/L [6]. The definition of metabolic syndrome (MetS) was adopted from the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP-ATP III) [7]. Subjects were diagnosed with MetS when they met any three or more of the following five components: 1) abdominal obesity (waist circumference > 90 cm in men or > 80 cm in women, the recommended criteria for Asian Americans), 2) high fasting blood glucose level (≥100 mg/dL), 3) high triglyceride level (≥150 mg/dL), 4) high SBP (≥ 130 mmHg) or DBP (≥ 85 mmHg), or 5) low HDL-C level (≤ 40 mg/dL in men or ≤ 50 mg/dL in women).

Data analysis

The data were expressed as mean ± standard deviation for continuous variables and percentages for categorical variables. The χ^2-test was used for comparing categorical characteristics of subjects and the Student`s *t*-test was used for the comparison of continuous variables of subjects. Univariate and

multivariate logistic regression were applied for analyzing the odds ratio (OR) of significant factors associated with hyperhomocysteinemia. A P value < 0.05 was considered as statistically significant. The SPSS software version 22.0 (IBM Corp., Armonk, NY, USA) was used for all analyses.

Results

The baseline characteristics of the participants enrolled in this study are presented in Table 1. The average age of 878 participants was 55.4 ± 10.8 years, and for gender, there were 535 females (60.9%) and 343 males (39.1%), while mean plasma Hcy level was 10.4 ± 3.64 μmol/L. The average level of metabolic factors of the 878 adults such as waist circumference (84.9 ± 10.9 cm), HDL-C (50.0 ± 13.4 mg/dL), triglyceride (136.6 ± 98.1 mg/dL), SBP (120.1 ± 20.4 mmHg), DBP (85.2 ± 11.7 mmHg) and sugar AC (104.9 ± 25.3 mg/dL) are also listed in the table.

Table 1. Baseline characteristics

Subjects were categorized into two groups by Hcy level (Table 2). Of the total 878, hyperhomocysteinemia was observed in 73 subjects. In participants with elevated Hcy level, the proportion of males was significantly higher than in a normal sample of Hcy level participants (94.5% versus 34.0%, $P < 0.001$). Besides, participants with high plasma Hcy had significantly higher waist circumference, triglyceride, SBP, DBP, sugar AC and significantly lower HDL-C as compared with those with normal plasma Hcy. The percentage of those with metabolic syndrome in the high Hcy group was also significantly higher than in the normal Hcy group (46.0% versus 32.5%, $P = 0.015$). Participants with elevated Hcy were more likely to be older and have higher uric acid level than control group subjects. BMI, total cholesterol, LDL-C, hs-CRP, lipoprotein showed no significant difference between the two groups.

Table 2. Differences between high homocysteine and normal homocysteine groups

Simple logistic regression analysis in Table 3 shows elevated Hcy was significantly associated with sex (OR 0.11, 95% CI 0.04-0.31, $P < 0.001$), age (OR 1.03, 95% CI 1.00-1.05, $P < 0.035$), waist circumference (OR 1.04, 95% CI 1.02-1.06, $P = 0.001$), HDL-C (OR 0.97, CI 0.95-0.99, $P = 0.011$), triglyceride (OR 1.00, CI 1.00-1.01, $P = 0.002$), SBP (OR 1.02, CI 1.01-1.03, $P = 0.004$), DBP (OR 1.04, CI 1.02-1.06, $P = 0.001$), sugar level (OR 1.01, CI 1.00-1.02, $P = 0.021$), uric acid (OR 1.39, CI 1.20-1.60, $P < 0.001$) and the presence of metabolic syndrome (OR 1.81, CI 1.12-2.93, $P = 0.016$). The multiple stepwise logistic regression analysis conducted with these factors showed that only sex (OR 0.15, CI 0.05-0.43, $P < 0.001$), age (OR 1.03, CI 1.00-1.05, $P = 0.036$), triglyceride (OR 1.002, CI 1.001-1.004, $P = 0.022$), SBP (OR 1.02, CI 1.00-1.03, $P = 0.023$) and uric acid (OR 1.26, CI 1.07-1.47, $P = 0.005$) were independently significantly associated with hyperhomocysteinemia.

Table 3. Regression analysis for association of high homocysteine with different variables

Discussion

This retrospective cross-sectional study revealed positive correlations between hyperhomocysteinemia and advanced age, triglyceride, blood pressure and uric acid levels. The subjects included in this current research were sampled from the Taiwanese population. Compared with a previous study based on Taiwanese people, the levels of average Hcy level were similar [8].

The positive relation between Hcy and triglyceride has been observed in several other studies as well. In research conducted in Japan with 40 patients diagnosed with type 2 diabetes mellitus, Hcy was associated with triglyceride but not with total cholesterol and LDL-C [9]. Momin et al. reported similar results based on a sample of 4660 Chinese in an urban community, with data that showed hyper-homocysteine state was independently related to elevated triglyceride [10]. The mechanism behind the relation between homocysteinemia and triglyceride has been proposed by several animal research studies. Experimental studies have suggested that Hcy-related endoplasmic reticulum stress increases the expression of sterol regulatory element-binding proteins (SREBPs), which further promote cholesterol and triglyceride synthesis [11]. The result was reproduced in an animal experiment by using methionine diet-fed mice, revealing elevated plasma triglyceride in increased plasma Hcy mice [12]. However, the relation between Hcy and triglyceride is not so consistent. Yadav et al. conducted a study involving 60 ischemic heart disease patients and failed to find a significant relationship between Hcy level and lipid profiles [13]. Another study enrolling 155 type 2 diabetes mellitus subjects also reported no significant association regarding hyperhomocysteinemia and high plasma triglyceride level [14].

Despite the inconsistent findings on the effect of Hcy, we provide a strong relation between elevated Hcy and triglyceride level in the current research. Some cross-sectional studies discussing the association between Hcy and lipid profiles other than triglyceride showed a negative relationship with HDL-C [9, 10, 15-19] and apolipoprotein [15-17, 20] but positive relationship with LDL-C [18]. The mechanism of Hcy related to decreased HDL-C and apolipoprotein has been demonstrated in animal models. Hcy down-regulated peroxisome proliferator-activated receptor (PPARα) and apolipoprotein AI protein level [21]. The result caused the suppression of lecithin-cholesterol acyltransferase substrate, which led to HDL maturation inhibition [22]. Significant relationship was noted between hyperhomocysteinemia and metabolic syndrome in our simple logistic regression analysis; however, the studies discussing the connection between Hcy and metabolic syndrome showed conflicting results. Seven hundred and twenty-two patients undergoing medical checkup in Korea revealed lack of association [23]. On the contrary, Esteghamati et al. found that homocysteine was correlated with metabolic syndrome based on a prospective study composed of 5893 subjects in Iran [24]. In our multiple stepwise logistic regression analysis, only some of the components of metabolic syndrome such as triglycerides and systolic blood pressure were independently significantly associated with elevated plasma homocysteine level. The differences between our analysis and prior studies were likely because of the adjusting variables we used, as our study also incorporated other cardiovascular disease risk factors including uric acid and CRP.

The connection between hyperhomocysteinemia and uric acid is explained by the methionine-homocysteine cycle [25]. In this cycle, methionine is converted to S-adenosyl-homocysteine (SAH), which becomes Hcy and adenosine, with adenosine then being degraded to uric acid. Therefore, an increase in

Hcy leads to an increase in uric acid level; this result is consistent with our analysis. Similar findings were also observed in other research studies [26, 27]. On the other hand, sex difference was also found to be an independent factor for elevated Hcy level in the current study, the mechanism of which might be related to the sex difference in Hcy metabolism. Normally, Hcy is metabolized by 2 different pathways: remethylation and transsulfuration [26]. A study involving 11 healthy young men and premenopausal women without cardiac risk factors conducted by Fukagawa et al. reported a significant higher rate of remethylation and a tendency toward higher rates of transmethylation in women than in men [28]. Therefore, it is reasonable to anticipate that Hcy level is higher in men than women.

An Indian study composed of 1243 healthy subjects confirmed the sex difference by showing a significantly higher level of Hcy over women [29]. In addition, creatine is synthesized from guanidinoacetate during the formation of SAH in the methionine-Hcy cycle. Creatine and subsequent creatinine synthesis is related to muscle mass, which provides an explanation for higher Hcy levels in men than women [30]. Hormonal difference has also been proposed as a reason contributing to the different Hcy levels in males and females. A clinical study with transsexuals showed that male-to-female subjects who were treated with ethinyl estradiol and antiandrogen had significantly decreasing levels of Hcy. On the contrary, female-to-male transsexuals who underwent testosterone treatment had increased plasma Hcy [31]. The age-related elevation of Hcy could be explained by the physiologically-associated renal function decline. A previous study concluded that glomerular filtration rates served as an important role in Hcy and creatinine clearance [32]. Possible mechanisms regarding the relationship between Hcy and blood pressure is that Hcy induces endothelial injury and oxidative stress, which leads to impaired nitric oxide release [33], and the consequences of these effects contribute to the raise of blood pressure.

There are several limitations in the current study. Firstly, the study is retrospectively designed, so further studies are needed to determine any causation. Secondly, the subjects were recruited from a single medical center, which might not represent the general population in Taiwan. Thirdly, participants who received medications for hypertension or hyperlipidemia were not excluded, so medication use might affect the result of our analysis.

Conclusions

Elevated serum homocysteine is associated with sex, age, uric acid and metabolic syndrome components. Among these factors, male gender, advanced age, triglyceride, systolic blood pressure and uric acid were profoundly associated with hyperhomocysteinemia. Further prospective cohort studies are needed for validating the influence on cardiovascular event prediction with homocysteine and its associates.

Abbreviations

BMI, body mass index; DBP, diastolic blood pressure; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MetS,

metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol.

Declarations

Ethics approval and consent to participate

The study was approved by the Chang Gung Medical Foundation Institutional Review Board. In this retrospective study, informed consent was unnecessary because the information of all participants was anonymized and de-identified.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

Study concept and design: PJC, YCL, PMW and SSL. Sampling and laboratory analysis: PJC, YCL and PMW. Statistical analysis and interpretation of data: SSL. Preparing the manuscript: PJC and SSL. Critical revision of the manuscript and corresponding author: SSL. All authors read and approved the final version of the manuscript.

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Tables

Table 1. Baseline characteristics

	Participants (n = 878)
Sex	
Female, n, %	535 (60.9%)
Male, n, %	343 (39.1%)
Age (years)	55.4±10.8
BMI (kg/m^2)	25.2±3.8
Waist circumference (cm)	84.9±10.9
Total cholesterol (mg/dl)	203.0±37.0
HDL-C (mg/dl)	50.0±13.4
Triglycerides (mg/dl)	136.6±98.1
LDL-C (mg/dl)	123.3±32.6
SBP (mmHg)	129.1±20.4
DBP (mmHg)	85.2±11.7
Sugar AC (mg/dl)	104.9±25.3
TC/HDL-C (mg/dl)	4.28±1.18
LDL-C/HDL-C (mg/dl)	2.62±0.92
Uric acid (mg/dl)	6.34±1.56
Plasma hs-CRP (ug/dl)	2.33±4.09

Plasma lipoprotein (mg/dl)	16.7±19.9
Plasma homocysteine (umol/l)	10.4±3.64

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

Table 2. Differences between high homocysteine and normal homocysteine groups

	High homocysteine (n=73)	Normal homocysteine (n= 805)	*P* value
Sex			<0.001*
Male, n, %	69 (94.5%)	274 (34.0%)	
Female, n, %	4 (5.5%)	531 (66.0%)	
Age (years)	58.2±9.9	55.2±10.9	0.034*
BMI (Kg/m^2)	25.9±4.1	25.2±3.8	0.140
Waist circumference (cm)	88.9±11.7	84.6±10.7	0.001*
Total cholesterol (mg/dl)	202±42.2	203.1±36.5	0.806
HDL-C (mg/dl)	46.2±12.0	50.4±13.5	0.011*
Triglycerides (mg/dl)	176.6±76.8	133.0±86.8	<0.001*
LDL-C (mg/dl)	122.2±37.8	123.4±32.1	0.764
SBP (mmHg)	135.7±19.7	128.5±20.4	0.004*
DBP (mmHg)	89.8±12.4	84.8±11.5	<0.001*
Sugar AC (mg/dl)	111.6±30.7	104.3±24.7	0.018*
TC/HDL-C	4.63±1.46	4.25±1.15	0.009*
LDL-C/HDL-C	2.81±1.09	2.60±0.91	0.062
Uric acid (mg/dl)	7.12±1.87	6.26±1.51	<0.001*
Hs-CRP (ug/dl)	3.15±6.73	2.25±3.76	0.076
Lipoprotein (mg/dl)	13.3±17.7	17.0±20.1	0.135
MetS, n, %			0.015*
yes	34(46.6%)	262(32.5%)	
no	39(53.4%)	543(67.5%)	

*: Indicates a significant difference, $p < 0.05$

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

Table 3. Regression analysis for association of high homocysteine with different variables

Variables	Simple logistic regression OR (95% CI)	*P* value	Multiple stepwise logistic regression OR (95% CI)	*P* value
Sex	0.11(0.04-0.31)	<0.001*	0.15(0.05-0.43)	<0.001*
Age	1.03(1.00-1.05)	<0.035*	1.03(1.00-1.05)	0.036*
BMI	1.05(0.98-1.11)	0.149		
Waist circumference	1.04(1.02-1.06)	0.001*		
Total cholesterol	1.00(1.00-1.01)	1.000		
HDL-C	0.97(0.95-0.99)	0.011*		
Triglyceride	1.00(1.00-1.01)	0.002*	1.002(1.001-1.004)	0.022*
LDL-C	1.00(0.99-1.01)	0.764		
SBP	1.02(1.01-1.03)	0.004*	1.02(1.00-1.03)	0.023*
DBP	1.04(1.02-1.06)	0.001*		
Sugar AC	1.01(1.00-1.02)	0.021*		
Uric acid	1.39(1.20-1.60)	<0.001*	1.26(1.07-1.47)	0.005*
Hs-CRP	1.04(0.99-1.08)	0.090		
Lipoprotein	0.99(0.97-1.00)	0.137		
MetS	1.81(1.12-2.93)	0.016*		

*: Indicates a significant difference, $p < 0.05$

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