Hyperhomocysteinemia Is Associated With Lipid Profiles and Lipid Ratio in Patients With Coronary Artery Disease

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Research Article

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Abstract

Objective: This study aimed to investigate the correlation of Hyperhomocysteinemia (HHcy) or serum homocysteine (Hcy) levels with lipid levels and lipid ratios in individuals with coronary artery disease(CAD).

Methods: A total of 1646 subjects with suspected CAD were divided into CAD or control groups. Serum Hcy, total cholesterol(TC), triglycerides(TGs), high-density lipoprotein cholesterol(HDL-C), low-density lipoprotein cholesterol(LDL-C), apolipoprotein(Apo)AI and ApoB concentrations were detected.

Results: Serum TC, LDL-C and ApoB in control subjects with HHcy were lower than those in individuals with normal Hcy, and serum HDL-C and ApoAI in CAD subjects with HHcy were lower than those in individuals with normal Hcy($P < 0.05$). The correlation analysis showed that serum TGs, LDL-C, ApoAI and HDL-C were correlated with Hcy($P <0.05$). There are different HHcy trends affecting the ratios of TC/HDL-C and LDL/HDL-C between the CAD and controls($P_{interaction}$ for TC/HDL-C=0.025; $P_{interaction}$ for LDL/HDL-C=0.033). CAD patients with HHcy had a higher ratio of TC/HDL-C(P=0.022) and LDL/HDL-C(P=0.045) than those with normal Hcy, but in the controls, the subjects with HHcy exhibited a trend toward a decreased ratio of TC/HDL-C(P=0.481) and LDL/HDL-C(P=0.303).

Conclusion: HHcy was related to the atherogenic lipid profile in patients with CAD. The lipid ratio is more suitable for assessing the effect of HHcy on CAD.

Introduction

Coronary artery disease (CAD) is the leading cause of death worldwide and remains a major health problem in both developed and developing countries [1]. Traditional lipid parameters, such as increased serum levels of total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein (Apo) B, or low levels of high-density lipoprotein cholesterol (HDL-C) and ApoAI, are among the most important modifiable risk factors for CAD [2, 3]. It has also been reported that nontraditional lipid profiles (lipid ratio) are a powerful predictor for cardiovascular disease (CVD) [4–13]. For instance, after a 10-year followed up of a prospective cohort study including 15,632 initially healthy US women, it was suggested that the TC/HDL-C ratio was as good as or better than apolipoprotein fractions for the prediction of future cardiovascular events [7]. TG/HDL-C is a highly atherogenic marker of insulin resistance and cardiometabolic risk and correlates positively with LDL phenotype B and LDL particle concentration and inversely with small, dense LDL particle size [9]. Moreover, TC/HDL-C and LDL-C/HDL-C have been found to be independent indicators of vascular risk with greater predictive value than isolated lipid levels [6–8, 12].

Despite therapeutic advances that control many risk factors, such as statins that have decreased LDL-C levels to lower levels than previously possible, CVD remains a major cause of morbidity and mortality worldwide [14]. Hyperhomocysteinemia (HHcy) has been regarded as a new risk factor for CVD. Folate

deficiency and the methylene tetrahydrofolate reductase (MTHFR) C677T polymorphism are considered the main causes of HHcy. In China, 1/4 of the population has the MTHFR C677T TT genotype, and due to dietary habits and the high prevalence of smoking and alcohol consumption, it is easy to lack folic acid, vitamin B6 and B12, thus resulting in HHcy in our population [15]. HHcy acts through various mechanisms, including vascular endothelium damage, stimulation of smooth muscle cell proliferation, and thrombosis activation [16, 17]. Previous studies have also established possible links among HHcy, dyslipidemia, and atherosclerosis [18–19]. Several studies relating HHcy to disturbed HDL-C metabolism have shown that Hcy can reduce circulating HDL-C by inhibiting ApoAI protein synthesis and enhancing HDL-C clearance [21–24].

In the present study, a negative correlation between HHcy and HDL-C and ApoAI was observed. However, perhaps due to the effects of lipid-lowering drugs, HHcy was also negatively associated with serum TC, TGs and ApoB. Therefore, it is difficult to determine whether HHcy promotes atherosclerosis or protects against atherosclerosis by evaluating traditional lipid parameters. Thus, this study aims to further investigate the association of HHcy with lipid ratio in CAD patients.

Materials And Methods

Objects

A total of 1646 patients with suspected CAD were recruited from a population of hospitalized patients in The People's Hospital of Guangxi Zhuang Autonomous Region. Coronary angiography (CAG) was performed in all enrolled subjects. Such as described in detail in our previous study[25], CAD was defined as significant coronary stenosis (≥ 50%) in at least one of the three main coronary arteries or their major branches (branch diameter ≥ 2 mm). Subjects with congenital heart disease, cardiomyopathy, valvular disease, autoimmune disease, or type I diabetes mellitus were excluded. The study protocol was approved by the Ethics Committee of The People's Hospital of Guangxi Zhuang Autonomous Region. Informed consent was obtained from all subjects after they received a full explanation of the study.

Blood sample collection and laboratory methods

After an overnight fast of at least 12 h, a venous blood sample was obtained from the forearm of each patient, which were described in detail in our previous study[26], serum Hcy was measured using an enzymatic cycling method. Serum TC, LDL-C, HDL-C, and TGs were measured by enzymatic methods with commercially available kits on a Beckman Coulter Automatic Analyzer. Serum ApoAI and ApoB levels were detected by immunoturbidimetric immunoassay. All of these biochemical analyses were performed at the Clinical Laboratory of The People's Hospital of Guangxi Zhuang Autonomous Region. According to results from previous studies [26], Hcy ≥ 15 μmol/L is often defined as HHcy.

Statistical analyses

The statistical software package SPSS 21.0 (SPSS Inc., Chicago, Illinois) was used for the statistical analyses. Quantitative variables are expressed as the mean ± standard deviation. Qualitative variables are expressed as raw counts and percentages. The differences in the general characteristics between patients and controls were tested by Student's unpaired t-test or chi-square analysis. Comparison of blood lipid parameters between different groups was performed by analysis of covariance (ANCOVA). Multivariate linear regression analysis with stepwise modeling was performed to evaluate the association of serum Hcy levels with serum lipid levels. Sex, age, and BMI were adjusted for the statistical analysis. A two-tailed P value of less than 0.05 was considered statistically significant.

Results

General characteristics and serum lipid levels

Table 1 shows the general characteristics and serum lipid parameters of the study population. Compared with the controls, the CAD patients had a higher proportion of males and individuals with hypertension, lower levels of HDL-C and ApoAI, and a higher level of serum Hcy (P for all < 0.05). Maybe due to the effects of lipid-lowering drugs, there were no significant differences in the levels of serum TC, TGs, LDL-C, or ApoB; there were also no significant differences in the age distribution or the prevalence of diabetes between the two groups (P > 0.05 for all).

Table 1
The general characteristics and serum homocysteine level in CAD and controls

Parameters	Controls	CAD	t/x^2	*P*
N	774	872	–	–
Age	63.66 ± 29.81	63.27 ± 10.40	0.362	0.730
Male/Female	432/342	634/238	51.273	0.000
Hypertension	198(25.6)	269(30.8)	5.598	0.018
Diabetes	88(11.4)	106(12.2)	0.244	0.621
TC (mmol/L)	4.53 ± 1.13	4.44 ± 1.22	1.654	0.097
TG (mmol/L)	1.56 ± 0.95	1.66 ± 1.12	-1.940	0.053
HDL-C (mmol/L)	1.15 ± 0.30	1.11 ± 0.32	2.467	0.014
LDL-C (mmol/L)	2.74 ± 0.80	2.66 ± 0.98	1.810	0.071
ApoAI (g/L)	1.18 ± 0.26	1.07 ± 0.31	7.350	0.000
ApoB (g/L)	0.91 ± 0.25	0.90 ± 0.29	0.277	0.780
Hcy(umol/l)	13.50 ± 5.84	15.11 ± 5.20	-5.928	0.000

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; Hcy: Homocysteine

Hyperhomocysteinemia and serum lipid levels

As shown in Table 2, when statistical analysis was performed between the normal Hcy and HHcy groups according to whether the serum homocysteine concentration was greater than 15 μmol/L, the levels of serum TC, LDL-C and ApoB in the HHcy group were significantly lower than those in the normal Hcy group; the levels of serum HDL-C and ApoAI in the HHcy group were significantly lower than those in the normal Hcy group (*P* for all < 0.05). There were no significant interactions between HHcy and disease in terms of the serum lipid levels (*P* for all > 0.05).

Table 2
HHcy and serum lipid levels in CAD patients and controls

Group	N	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoAI (g/L)	ApoB (g/L)
Control							
Normal Hcy	532	4.60 ± 1.20	1.61 ± 0.99	1.16 ± 0.31	2.80 ± 0.83	1.19 ± 0.26	0.92 ± 0.26
HHcy	242	4.37 ± 0.94	1.46 ± 0.83	1.13 ± 0.27	2.61 ± 0.66	1.16 ± 0.24	0.88 ± 0.21
F		6.856	3.677	1.827	9.039	2.119	5.013
P		0.009	0.056	0.177	0.003	0.146	0.025
CAD							
Normal Hcy	484	4.49 ± 1.32	1.69 ± 1.20	1.15 ± 0.30	2.70 ± 1.05	1.10 ± 0.25	0.91 ± 0.31
HHcy	388	4.37 ± 1.06	1.63 ± 1.01	1.07 ± 0.34	2.62 ± 0.86	1.04 ± 0.37	0.89 ± 0.25
F		1.783	0.525	10.202	1.279	6.197	0.650
P		0.182	0.469	0.001	0.258	0.013	0.420
P interaction		0.303	0.615	0.382	0.240	0.667	0.363

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; HHcy: Hyperhomocysteinemia; Hcy: Homocysteine

HHcy and nontraditional lipid profiles (lipid ratios)

As shown in Table 3, there are different trends in HHcy affecting the ratio of TC/HDL-C and LDL-C/HDL-C between the CAD patients and controls ($P_{interaction}$ for TC/HDL-C = 0.025; $P_{interaction}$ for LDL-C/HDL-C = 0.033). CAD patients with HHcy had a significantly higher ratio of TC/HDL-C than those with normal Hcy (normal Hcy: 4.10±1.32 *vs* HHcy: 4.43±2.60, P = 0.025), but in the controls, the subjects with HHcy exhibited a trend toward a decreased ratio of TC/HDL-C (normal Hcy: 4.11±1.03 *vs* HHcy: 4.05±1.11, P = 0.481). CAD patients with HHcy had a higher ratio of LDL/HDL-C (normal Hcy: 2.48±1.07 *vs* HHcy: 2.65±1.36; P = 0.045), but in the controls, the subjects with HHcy exhibited a trend toward a decreased ratio of LDL/HDL-C (normal Hcy: 2.52±0.80 *vs* HHcy: 2.45±0.85; P = 0.303).

Table 3

Lipid ratios in the HHcy and normal Hcy groups

Group	N	TC/HDL-C	TG/HDL-C	LDL/HDL-C	ApoB/ApoAI
Control					
Normal Hcy	532	4.11±1.03	1.50±1.02	2.52±0.80	0.80±0.27
HHcy	242	4.05±1.11	1.43±1.00	2.45±0.85	0.79±0.27
F		0.498	0.781	1.063	0.210
P		0.481	0.377	0.303	0.647
CAD					
Normal Hcy	484	4.10±1.32	1.60±1.27	2.48±1.07	0.87±0.35
HHcy	388	4.43±2.60	1.79±2.18	2.65±1.36	0.92±0.36
F		5.276	2.431	3.860	4.372
P		0.022	0.119	0.045	0.037
P interaction		0.025	0.144	0.033	0.094

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; HHcy: Hyperhomocysteinemia

Correlation of Hcy and serum lipid parameters

The correlation between the Hcy and serum lipid parameters is shown in Table 4. Sex, age, BMI, diabetes, and hypertension were excluded from the statistical analysis. The serum LDL-C and ApoAI levels were correlated with Hcy in the combined CAD and control populations ($P < 0.05$). The levels of serum HDL-C and TGs in the control group and HDL-C and ApoAI were correlated with Hcy ($P < 0.05$ for each).

Table 4
Correlation of the Hcy and serum lipid parameters

Relative factor	Unstandardized coefficient	Std. error	Standardized coefficient	*t*	*P*
Total					
LDL-C	-0.465	0.152	-0.075	-3.053	0.002
ApoAI	-2.458	0.482	-0.125	-5.097	0.000
Control					
TG	-0.616	0.223	-0.100	-2.768	0.006
HDL-C	-1.614	0.706	-0.083	-2.287	0.022
CAD					
HDL-C	-1.499	0.624	-0.092	-2.404	0.016
ApoAI	-1.652	0.668	-0.095	-2.473	0.014

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoAI, apolipoprotein AI; ApoB, apolipoprotein B

Discussion

CAD is one of the leading causes of morbidity and mortality worldwide. Despite best efforts, available therapies protect only 30–40% of individuals at risk [14]. Thus, it is important to investigate new predictors of CAD to help protect against and provide a new treatment for CAD. A possible relationship between HHcy and CAD was first suggested by Wilcken and Wilcken in 1976 [27]. Since then, more data from various epidemiological investigations and laboratory studies have demonstrated that an increased concentration of serum Hcy was considered to be an independent risk factor for CVD. A meta-analysis showed that an increase of 5 μmol/L in plasma homocysteine level enhances the risk of CVD by 1.6- to 1.8-fold, which is similar to the risk seen with an increase of 20 mg/ dL (0.52 mmol/L) in cholesterol concentration [28]. However, the mechanism for this risk remains unclear. It is well known that serum lipid levels are the most important risk factors for CAD. In the present study, perhaps due to the effects of lipid-lowering drugs, there were no significant increases in the levels of serum TC, TGs, LDL-C, or ApoB in CAD patients, but the serum HDL-C and ApoAI were lower in the CAD patients. We also found that serum Hcy was higher in CAD patients. Therefore, we speculate that HHcy may affect the occurrence of CAD by affecting the blood lipid profile, especially HDL-C and ApoAI.

In the present research, statistical analysis was performed between normal Hcy and HHcy groups according to whether the serum homocysteine concentration was greater than 15 μmol/L. The levels of serum TC, LDL-C and ApoB in control subjects with HHcy and the levels of serum HDL-C and ApoAI in CAD subjects with HHcy were significantly lower than those of individuals with normal Hcy (*P* for all <

0.05). There were also some invaluable clinical observations that demonstrate the possible link between Hcy and lipid metabolism pathways. Most research findings suggest that Hcy is significantly and negatively correlated with HDL-C and ApoAI in CAD or community-based populations. HDL and ApoAI exert anti-atherogenic effects by transporting cholesterol from cells into peripheral tissues [29], reducing oxidative stress and suppressing inflammatory pathways [30]. Low ApoAI (HDL-C) levels are a risk factor for atherosclerosis. Recent animal and in vitro cell studies have also demonstrated that Hcy suppresses hepatic ApoAI expression via the peroxisome proliferator-activated receptor α (PPARα)-ApoAI pathway [24]. Moreover, Hcy could decrease the transcription of ApoAI by stimulating nuclear factor κB (NF-κB) and ApoAI regulatory protein-1 (ARP-1) [23] and enhancing HDL cholesterol clearance [22]. These increased Hcy levels may impair cardiovascular function via the inhibition of ApoAI expression and the impairment of its antioxidant capacity [21]. In the present study, although the subjects enrolled in this study had been treated with statins prior to angiography, it is well known that the effect of statins on blood lipids is mainly reflected by lower TC and LDL-C levels and less on HDL-C and ApoAI levels. The negative correlation between HHcy and HDL-C and ApoAI was confirmed by multivariate regression analysis, which suggests that serum Hcy may promote CAD by disturbing HDL (ApoAI) metabolism.

The interaction between Hcy and serum TC, TGs and LDL-C has been explored in some small sample clinical observation studies. Durdi et al. reported that in 126 myocardial infarction patients, Hcy was positively correlated with LDL-C levels [31]. In 300 Indian subjects with proven CAD, Hcy was found to be positively associated with TGs and very low-density lipoprotein cholesterol (VLDL-C) [32]. In northern Chinese subjects, the prevalence of HHcy in the combined hyperlipidemia group was reported to be significantly higher than that in the control group, with an OR of 3.339 [33]. There are also two community-based studies that incorporated large samples in China; Momin M et al. showed that HHcy was independently associated with hypertriglyceridemia [34], and Qin YY et al. showed that HHcy was related to high concentrations of TC, TGs, and LDL-C [35]. However, not all prior studies have found correlations between HHcy and lipid profiles [36, 37]. Importantly, the most recent data, including 18297 US adults from the Very Large Database of Lipids (VLDL-21), indicate that, in unadjusted analysis, levels of LDL-C and non-HDL-C were lower, whereas levels of TGs and VLDL-C were higher in the highest Hcy quartile, but after adjusting for confounders, the associations disappeared [38]. In the present study, we found that the levels of serum TC, LDL-C and ApoB in the HHcy group were significantly lower than those in the normal Hcy group in a population treated with lipid-lowering therapy, which appears to suggest that Hcy is associated with lipid parameters in the protection against atherosclerosis in these populations. To explain these contradictions, it must be noted that information on lipid-lowering medication, one of the most important confounders, was uncertain in our study and the VLDL-21 study. Perhaps it is very interesting to explore why individuals with HHcy who are taking lipid-lowering drugs have healthier blood lipid profiles. However, we lack information about the dose and treatment course of lipid-lowering drugs and the baseline lipid level before treatment. The effect of the interaction between HHcy and lipid-lowering drugs on blood lipids needs further research to clarify. Therefore, it is difficult to determine

whether HHcy promotes atherosclerosis or protects against atherosclerosis by evaluating indicators such as TC, LDL and ApoB that are greatly affected by lipid-lowering drugs.

Nontraditional lipid profiles, including TC/HDL-C, LDL/HDL-C, TG/HDL-C and ApoB/AI, have been found to be independent indicators of vascular risk with greater predictive value than isolated lipid levels. Our current study aimed to evaluate whether HHcy is associated with promoting atherosclerosis or protecting against atherosclerotic lipid profiles by evaluating the lipid ratio. The present study showed that different trends in Hcy affect the ratio of TC/HDL-C and LDL-C/HDL-C between the CAD and controls (P for interaction < 0.05). In the controls, HHcy was associated with a decreased trend in the ratio of TC/HDL-C (normal Hcy: 4.11 ± 1.03 *vs* HHcy: 4.05 ± 1.11; P = 0.481) and LDL/HDL-C (normal Hcy: 2.52 ± 0.80 *vs* HHcy: 2.45 ± 0.85; P = 0.303). However, CAD patients with HHcy had a significantly higher ratio of TC/HDL-C (normal Hcy: 4.10 ± 1.32 *vs* HHcy: 4.43 ± 2.60; P = 0.025) and higher LDL/HDL-C (normal Hcy: 2.48 ± 1.07 *vs* HHcy: 2.65 ± 1.36; P = 0.045) than normal Hcy patients. The importance of TC/HDL-C and LDL/HDL-C was highlighted in some large studies; Ridker PM showed that the use of either the ratio of TC/HDL-C or that of LDL/HDL-C is superior to the use of TC or LDL-C alone [7]. Arsenault BJ et al. observed that among apparently healthy men and women in a cohort representative of a contemporary Western population, the TC/HDL-C ratio was more strongly associated with the risk of future CHD than LDL-C; they also found that at any LDL-C level, individuals with an elevated TC/HDL-C ratio were still at an increased risk of developing CAD [6]. Therefore, these findings suggest that HHcy may play an important role in the atherogenic lipid profile in patients with CAD. In people taking lipid-lowering drugs, the ratio of blood lipids is more suitable for assessing the effect of HHcy on CAD.

Conclusion

The traditional lipid levels of serum TC, LDL-C, and ApoB in control subjects with HHcy and serum HDL-C and ApoAI in CAD subjects with HHcy were significantly lower than those in individuals with normal Hcy. The effect of HHcy on the ratio of TC/HDL-C and LDL/HDL-C was different between the CAD patients and controls. HHcy was related to the atherogenic lipid ratio in patients with CAD. The ratio of blood lipids is more suitable for assessing the effect of HHcy on CAD.

Abbreviations

Apo: Apolipoprotein

Apo: ApoAI regulatory protein-1

CVD: Cardiovascular disease

CAD: Coronary artery disease

Hcy: Homocysteine

HHcy: Hyperhomocysteinemia

HDL-C: High-density lipoprotein cholesterol

MTHFR: Methylene Tetrahydrofolate Reductase

LDL-C: Low-density lipoprotein cholesterol

NF-Kb: Nuclear factor κB

PPARα: Peroxisome proliferator-activated receptor α

TG: Triglycerides

TC: Total cholesterol

VLDL-C: Very low-density lipoprotein cholesterol

Declarations

Ethics approval and consent to participate

This study was complied with the Declaration of Helsinki and approved by the Institutional Ethics Committee of People's Hospital of Guangxi Zhuang Autonomous Region. Written informed consent was not obtained from the participants, because of the data retrospectively obtained from electronic medical records.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable requests after study completion.

Competing interests

None

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Authors' contribution

DFW participated in the design, performed the statistical analyses, and drafted the manuscript. JLD conceived the study, participated in the design. QCL, FL, ZW, KY collected the data and the samples. All authors read and approved the final manuscript.

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