Increased levels of serum Hcy and UA as well as the thickness of carotid intima-media correlates with the severity of coronary artery lesions

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Abstract

Background To investigate the correlation between serum homocysteine (Hcy) and uric acid (UA) levels as well as carotid intima-media thickness (IMT) and the severity of coronary artery lesions in elderly patients with coronary heart disease (CHD). **Methods** A total of 156 elderly patients with CHD in the experimental group were further divided into low, middle and high score groups. Serum Hcy and UA levels, IMT, Gensini and Sullivan scores were measured and analyzed by Pearson correlation. The risk factors for CHD and the correlation were analyzed by single factor analysis and logistic regression. **Results** The serum levels of Hcy, UA and the IMT in the experimental group were significantly higher than those in the control group (all $P < 0.001$). Gensini scores showed that the levels of serum Hcy, UA, and the IMT in middle and high score groups were significantly higher than those in the low score group, while the high score group had the significant highest level (all $P < 0.001$). Serum Hcy, UA levels and the IMT were positively correlated with Gensini and Sullivan scores (all $P < 0.001$). And male gender, smoking, history of hypertension, systolic pressure, pulse pressure, Hcy, UA, IMT, and BMI were independently correlated with the severity of CHD (all $P < 0.05$). **Conclusions** The serum levels of Hcy and UA and the IMT in patients with CHD were significantly increased, and were positively correlated with the severity of coronary artery lesions, which may serve as diagnostic indicators.

Background

Coronary heart disease (CHD) is a common disease of circulatory system. It is caused by many factors including the person's living environment, dietary habits, heredity and so on. Coronary atherosclerotic heart disease, the most common type of CHD, is caused by coronary atherosclerotic stenosis, which leads to necrosis of the myocardium due to the insufficient blood supply. In addition, broadly speaking, the stenosis of the lumen caused by extensive inflammation and embolism also belong to CHD. For a long time, the "gold standard" for evaluating the severity of coronary artery lesions has been the coronary angiography, but it is too traumatic to be suitable for elderly patients. However, most CHD patients are middle-aged and elderly. Therefore, it is important to identify and develop appropriate non-invasive tests and indicators for clinical evaluation of the severity of CHD.

In recent years, it has been shown that the severity of CHD coronary artery lesions is related to the levels of serum homocysteine (Hcy) and uric acid (UA) and the carotid intima-media thickness (IMT) [1]. Hcy is a sulfur-containing amino acid produced during methionine metabolism and is significantly associated with the severity of coronary artery lesions. It plays an important role in the development of cardiovascular diseases such as atherosclerosis, aneurysm and myocardial infarction [2]. Hcy can promote hypertrophy and proliferation of neutrophils, which can directly damage vascular endothelial cells and their function, thereby, increasing the risk of cardiovascular disease. As a specific component of the cardiovascular structure, UA is one of the most important water-soluble endogenous antioxidants in the human body [3]. UA can aggravate atherosclerosis by promoting renal tubule reabsorption of sodium ions. Some studies have shown that UA is an independent risk factor and an independent predictor of coronary atherosclerosis [4]. It's also suggested that UA has a protective effect due to its free radical

scavenging effect which is 10 times better than that of other anti-oxidants [5]. It can chelate metal ions and inhibit the Fenton reaction. It can, hence, prevent cardiovascular damage by oxidative stress and thus play a protective role. It is considered that the lowering UA level can improve the prognosis of CHD patients with acute myocardial infarction. A study found that when coronary atherosclerosis occurs, the IMT increases [6]. IMT can be easily and noninvasively measured to observe atherosclerosis in patients with CHD and is a good indicator of the severity of coronary artery lesions. The most important characteristics of CHD are irreversibility, sudden death rate and a slow disease progression. Therefore, early diagnosis and treatment of CHD is of great importance. What's more, the diagnosis of the severity of CHD mainly depends on the assessment of the severity of coronary artery lesions [7]. This diagnosis can help in appropriate treatment and prognosis of CHD. Hence, in the present study, we have explored the correlation between serum levels of Hcy and UA as well as the IMT, and the severity of coronary artery lesions in elderly patients with CHD.

Methods

General data

This study was approved by the Medical Ethics Committee of The Second Xiangya Hospital of Central South University. A total of 156 elderly patients admitted in our hospital for CHD diagnosed by coronary angiography from September 2017 to August 2018 were enrolled as the experimental group for retrospective analysis. According to their Gensini scores, the experimental group was further sub-divided into three groups: low score (≤ 20 points, 72 cases), middle score (21–40 points, 56 cases) and high score (≥ 40 points, 28 cases) groups [8]. Another 54 healthy controls with normal coronary artery were enrolled as the control group. All patients and their families agreed to participate in the study and signed the informed consent document.

Inclusion criteria: All patients: (1) met the diagnostic criteria of CHD according to the *Guidelines for Coronary Heart Disease*, and were diagnosed by coronary angiography [9]; (2) were aged from 61 to 88 years; (3) had no history of an operation, hormone use, use of immunosuppressive agents and antibiotics in the past six months; (4) had no history of gout and hyperuricemia.

Exclusion criteria: The following patients were excluded: (1) those with serious diseases of liver, kidney, brain, lung and other basic organs; (2) those with acute and chronic infections; (3) those with malignant tumors, tuberculosis and aneurysms; (4) those with diseases of blood, endocrine and immune systems; and (5) those with lactation and pregnancy.

Sample collection

Following enrollment, 5 mL of fasting venous blood was collected from all study participants and after 30 min, centrifuged at a speed of 3,000 rpm for 10 minutes. The serum was used to determine the Hcy and UA levels in the blood. The serum Hcy level was measured using circulating enzyme method with Hcy

detector (Shenzhen AUSA Pharma Co., Ltd.) according to the kit instructions (Shanghai Jimian Industrial Co., Ltd.). UA enzyme colorimetry was used to measure serum UA level by automatic biochemical analyzer according to kit instructions (Shanghai Xinfan Biotechnology Co., Ltd.). VIVID7 ultrasound diagnostic device (Shenzhen Kaili Biomedical Science and Technology Co., Ltd.) was used to examine the carotid arteries in the subjects in the supine position with the probe frequency ranging from 7.5 Hz to 12.0 Hz.

Observation parameters

Main parameters: (1) The levels of Hcy, UA and IMT: The levels of Hcy, UA and IMT were compared between the experimental group and control group as well as among low, middle and high score group. IMT was measured as the mean of thickness between the anterior and posterior walls of the carotid arteries, including bilateral carotid bifurcation, bilateral internal carotid artery and the bilateral of the common carotid artery. It was evaluated that $0.9 \text{ mm} \leq \text{IMT} < 1.3 \text{ mm}$ was considered as thickening while $\text{IMT} \geq 1.3 \text{ mm}$ was considered as atheromatous plaque formation. (2) Gensini score: All experimental group patients underwent coronary angiography by Judkins method in the catheter room of our hospital. According to the segmentation evaluation standard for the coronary artery image score of the American Heart Association, the integral for each lesion equaled the stenosis score multiplied by the lesion site integral. Each patient's score was the sum of the integral for each lesion (Gensini score) [9]. The higher the score was, the greater the degree of coronary artery stenosis was.

Secondary parameters: (1) Sullivan score: The proportion of coronary intima atherosclerotic plaque was evaluated by Sullivan score, which was positively correlated with Sullivan score. (2) The general data of experimental group and control group were included in the single factor analysis, including gender, body mass index (BMI), history of smoking, alcohol consumption, hypertension, diabetes and cardiovascular diseases, systolic, diastolic and pulse pressure, Hcy, UA and IMT. (3) The correlation of multiple factors and severity of coronary artery lesions.

Statistical methods

All data in this study were analyzed by SPSS21.0 statistical software. The level of each observation index was expressed as the mean $\pm$ standard deviation ($\pm$ sd) and analyzed using F-test. All count data were expressed as percentages (n, %) and analyzed using a χ^2 test. Pearson linear correlation analysis was used to analyze the correlation between serum Hcy, UA level as well as IMT and Gensini score, Sullivan score. The general data of experimental group and control group were included in the single factor analysis. Logistic regression analysis was used to analyze the correlation of multiple factors and severity of coronary artery lesions. The integral of coronary stenosis was taken as the dependent variable while Hcy, UA and IMT were taken as independent variables. Differences were considered significant when $P < 0.05$.

Results

General data comparison among low, middle and high score groups

There was no significant difference in the general data among the three groups ($P > 0.05$), as shown in Table 1.

Comparison of Hcy and UA levels and IMT among low, middle and high score groups

The serum Hcy, UA and the IMT in the middle and high score groups were significantly higher than those in the low score group (all $P < 0.001$), while those in the high score group were significantly higher than those in the middle score group (all $P < 0.001$), as shown in Table 2 and Fig. 1.

Correlation of serum Hcy, UA level and IMT with Gensini score

Pearson correlation analysis showed that serum Hcy and UA levels and IMT were positively correlated with Gensini score in the experimental group ($r = 0.476, 0.517, 0.528$; $P < 0.001$), respectively, as shown in Table 3 and Fig. 2.

Correlation of serum Hcy and UA levels and IMT with Sullivan integral

Pearson correlation analysis showed that serum Hcy and UA levels and IMT were positively correlated with Sullivan integral in the experimental group ($r = 0.587, 0.563, 0.617$; $P < 0.001$), respectively, as shown in Table 4 and Fig. 3.

Univariate analysis of general data in the experimental and control groups

Univariate analysis of the general data showed that male gender, BMI, history of smoking, history of hypertension, systolic blood pressure, pulse pressure, Hcy, UA, and IMT were significantly correlated with CHD in the experimental group (all $P < 0.05$), as shown in Table 5.

Logistic regression analysis of the correlation between multivariate factors and CHD

Based on assignment table (Table 6), logistic regression analysis showed that male gender, smoking, history of hypertension, systolic blood pressure, pulse pressure, Hcy, UA, IMT, and BMI independently correlated with the severity of CHD in the experimental group (all $P < 0.05$). See Table 7.

Discussion

There are many risk factors for developing CHD in the elderly, among which age is the most significant, followed by carotid plaque formation. In addition, B-complex vitamins, gender, obesity, smoking and alcohol can affect the severity of coronary artery disease by influencing the level of serum Hcy and UA [10]. In recent years, with the increasing incidence and mortality of CHD in the elderly, the improvement of therapeutic efficacy has been the heat spot. Under the circumstance of slow progression and high risk of late stage, the key to the effective management of CHD is timely and effective diagnosis. Studies have shown that the main method to assess the severity of CHD in patients is to evaluate the severity of coronary artery lesions, so it is important to find suitable non-invasive, low-cost evaluation markers [11].

Hcy is produced in the liver and other organs by methionine metabolic cycle. There are two ways, methionine and cysteine. Normally, Hcy has a lower serum level about 8 μmol [12]. Hcy induces coronary artery disease by damaging proteins through oxidative stress, resulting in the decrease or inactivation of enzymes and enzyme receptors, along with the decrease in nitric oxide synthesis, and subsequently impairs endothelial function, ultimately hindering vascular expansion. Besides, Hcy is an important factor in promoting thrombosis. Under its increased expression, the blood is in a hypercoagulable state, which causes a large number of platelets to adhere and aggregate together. At the same time, Hcy induces lumen stenosis by stimulating the proliferation of vascular smooth muscle cells, and also results in an imbalance in the lipid, carbohydrate and protein metabolism, leading to the formation of lipid deposition plaques [13, 14]. The observations in our study showed that the serum Hcy level in the CHD group was significantly higher than in the control group, indicating that the serum Hcy level was an independent risk factor for CHD. The study also showed that the level of serum Hcy in high and middle score groups was significantly higher than in low score group and that in high score group was even higher as compared to the middle score group. This indicated that the level of serum Hcy was positively correlated with Gensini score, namely, the severity of coronary lesions. The higher the level of serum Hcy, the more serious the coronary lesions. Various studies have found that there is a significant correlation between high serum Hcy level and CHD [15]. Wang et al. also found the significant correlation between serum Hcy level and severity of coronary artery disease [16]. These previous results are consistent with the observations in this study [17, 18].

UA is a water-soluble antioxidant distributed in the human cardiovascular system, which is normally stable in the serum. It is produced by purine metabolism by the oxidation of hypoxanthine to xanthine under the action of enzymes and finally to UA [19]. Some studies have pointed out that serum UA levels in the elderly diagnosed with CHD show significant changes, suggesting that it has a certain correlation with coronary artery disease [20]. In elderly CHD coronary artery disease, UA level increased as a result of increasingly producing but slowly clearing. Studies have shown elevated serum UA level can lead to sympathetic excitation and renal hemodynamic changes. To be specific, UA promotes the re-absorption of sodium through the proximal convoluted tubules of the glomeruli and accelerates the production of endothelin in blood, thus inducing CHD and also aggravating the severity of coronary artery disease [21]. This study showed that the serum UA levels in experimental group was significantly higher than in control

group, and the serum UA level in high and middle score groups was significantly higher than that in the low score group and high score group had the highest serum UA level. This indicated that serum UA is an independent risk factor for CHD and was positively correlated with the severity of coronary artery disease, which was consistent with the above findings [22].

IMT is an important visual index for evaluating the severity of coronary artery disease. A study has shown that IMT is correlated with the severity of coronary artery disease and greater the IMT, the more serious CHD [23]. One of the pathological basis for developing CHD in the elderly is endothelial damage, which leads to lipid deposition under the intima of the vessel, promotes inflammation and plaque formation, and eventually thickens smooth muscle and hardens the vessel wall, leading to increased IMT [24]. In this study, IMT in the experimental group was significantly higher than that in the control group; IMT in middle and high score groups was significantly higher than that in low score group; while IMT in high score group was significantly higher than that in middle score group, indicating that IMT is significantly correlated with the severity of coronary artery disease. The results were consistent with those of the above studies [25].

Pearson correlation analysis showed that serum Hcy, UA level and IMT were positively correlated with Gensini and Sullivan score, respectively. Logistic regression analysis showed that male gender, smoking, history of hypertension, systolic blood pressure, pulse pressure, Hcy, UA, IMT and BMI were independently associated with the severity of CHD. The greatest disadvantage of this study is the small sample size.

Conclusions

In conclusion, the levels of serum Hcy and UA and IMT in patients with CHD were significantly increased, and the increase was positively correlated with the severity of coronary artery lesions. They can be used as diagnostic indices for evaluating the severity of CHD in clinical settings.

Abbreviations

Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness; CHD, coronary heart disease; BMI, body mass index

Declarations

Ethical approval and consent to participate

This study was approved by the Medical Ethics Committee of The Second Xiangya Hospital of Central South University. All patients and their families agreed to participate in the study and signed the informed consent document.

Consent for publication

Not applicable.

Availability of data and materials

The analysed data sets generated during the study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CMT contributed to the study concepts, study design, definition of intellectual content, literature research and data acquisition in addition to preparing and editing the manuscript. JML contributes to the manuscript review and guaranteed the integrity of the entire study. FX contributed to data and statistic analysis. CMT carried out the clinical studies. FX and YZZ did experimental studies. The final version of the manuscript has been read and approved by all authors, and each author believes that the manuscript represents honest work.

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Tables

Table 1 General data comparison ($\pm$ sd, n (%))

Group	Low score group (<i>n</i> = 28)	Middle score group (<i>n</i> = 28)	High score group (<i>n</i> = 28)	F	P
Gender (male/ female)	55/17	42/14	22/6	0.243	0.912
Average age (year)	71.91±13.82	71.21±14.12	73.32±14.11	0.831	0.312
BMI (kg/m ²)	24.43±2.34	24.35±2.31	24.65±2.37	0.217	0.918
Type of CHD (<i>n</i> , %)					
Stable type	30 (41.67)	23 (41.07)	11 (39.29)	0.047	0.977
Unstable type	19 (26.39)	15 (26.79)	8 (28.57)	0.05	0.976
Acute cardiac infarction	23 (31.94)	18 (32.14)	9 (32.14)	0.001	1.000
Complications (<i>n</i> , %)					
Hypertension	40 (55.56)	31 (55.36)	16 (57.14)	0.267	0.987
Diabetes	29 (40.28)	24 (42.86)	11 (39.29)	0.128	0.937
Hyperlipidaemia	43 (59.72)	34 (60.71)	17 (60.71)	0.016	0.992

BMI, body mass index; CHD, coronary heart disease.

Table 2 Comparison of Hcy and UA levels and IMT ($\pm$ sd)

Group	Low score group (<i>n</i> = 28)	Middle score group (<i>n</i> = 28)	High score group (<i>n</i> = 28)
Hcy (μ mol/L)	11.34 $\pm$ 6.83	20.03 $\pm$ 7.88 ^{***, ###}	28.98 $\pm$ 8.04 ^{***}
UA (μ mol/L)	206.78 $\pm$ 77.45	326.34 $\pm$ 79.34 ^{***, ###}	456.67 $\pm$ 98.34 ^{***}
IMT (mm)	1.19 $\pm$ 0.05	1.26 $\pm$ 0.07 ^{***, ###}	1.33 $\pm$ 0.08 ^{***}

^{***}P<0.001, compared with low score group; ^{###}P<0.001, compared with high score group.

Table 3 Correlation of serum Hcy, UA level and IMT with Gensini score

Group	Correlation coefficient	Statistic	P
Hcy	0.476	10.069	0.000
UA	0.517	10.091	0.000
IMT	0.528	10.031	0.000

Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Table 4 Correlation of serum Hcy and UA levels and IMT with Sullivan score

Group	Correlation coefficient	Statistic	P
Hcy	0.587	10.031	0.000
UA	0.563	10.043	0.000
IMT	0.617	10.034	0.000

Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Table 5 Univariate analysis of general data

Group	Control group (<i>n</i> = 54)	Experimental group (<i>n</i> = 150)	P	χ^2
Male (<i>n</i> , %)	23 (42.59)	119 (76.28)	0.000	24.254
BMI (kg/m ²)	30.21±4.13	24.32±2.12	0.000	10.033
Smoking (<i>n</i> , %)	33 (61.11)	60 (38.46)	0.004	8.340
Drinking (<i>n</i> , %)	10 (18.52)	21 (13.46)	0.367	0.815
Hypertension history (<i>n</i> , %)	10 (18.52)	105 (67.31)	0.000	38.545
Diabetes history (<i>n</i> , %)	8 (14.81)	16 (10.26)	0.364	0.823
CVD history (<i>n</i> , %)	12 (22.22)	35 (22.44)	0.974	0.001
Systolic pressure (mmHg)	122.21±8.32	135.32±11.34	0.000	9.033
Diastolic pressure (mmHg)	76.34±5.43	75.34±8.32	0.317	1.005
Pulse pressure (mmHg)	45.43±10.32	60.12±12.32	0.000	8.560
Hcy (μmol/L)	7.59±0.46	21.03±7.66	0.000	21.801
UA (μmol/L)	155.33±47.79	363.35±85.31	0.000	22.057
IMT (mm)	0.81±0.05	1.28±0.07	0.000	53.317

BMI, body mass index; CVD, cardiovascular disease; Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Table 6 Univariate analysis of general data

Index	Assignment	
	0	1
Gender	Female	Male
Body mass index (kg/m ²)	≥26	<26
Smoking	No	Yes
Hypertension history	No	Yes
Systolic pressure (mmHg)	≤128	>128
Pulse pressure (mmHg)	≤52	>52
Hcy (μmol/L)	≤11	>11
UA (μmol/L)	≤190	>190
IMT (mm)	≤1	>1

Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Table 7 Logistic regression analysis of the correlation between multivariate factors and CHD

Index	OR	95% CI	P
Male	10.22	1.23-70.32	0.000
Body mass index	9.21	2.21-61.24	0.000
Smoking	10.23	2.21-31.22	0.000
Hypertension history	9.32	1.12-33.42	0.000
Systolic pressure	11.33	2.21-32.33	0.000
Pulse pressure	11.35	2,22-32.22	0.000
Hcy	10.88	1.38-71.43	0.000
UA	11.21	2.13-61.13	0.000
IMT	12.35	5.08-31.02	0.000

CHD, coronary heart disease; OR, odds ratio; CI,confidence interval; Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness.

Figures

Figure 1

Fig. 1 Comparison of Hcy(A), UA (B) and IMT (C) levels among low, middle and high groups. Compared with the low group, ***P<0.001; compared with the high group, ###P<0.001. Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness

Figure 2

Fig. 2 Correlation between serum Hcy (A), UA (B) levels and IMT (C) and Gensini scores. Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness

Figure 3

Fig. 3 Correlation between serum Hcy (A), UA (B) levels and IMT (C) and Sullivan scores. Hcy, homocysteine; UA, uric acid; IMT, intima-media thickness