CORRELATION BETWEEN SERUM FERRITIN AND PREMATURE CORONARY ARTERY DISEASE IN MIDDLE-AGED MALE PATIENTS WITH 5 YEARS OF FOLLOW-UP

XIAOXIAO CHANG
School of nursing, Shanghai Jiguang Polytechnic College

ABSTRACT

Purpose*: To investigate the correlation between serum ferritin levels and clinical outcomes of premature coronary artery disease (PCAD) in middle-aged male patients.*

Methods*: A total of 420 middle-aged male patients with PCAD were recruited with case-control method for this study. The patients were grouped into two based on the cut off serum ferritin (SF) ≥ 200 ng/m: overload group (SF ≥ 200 ng/ml) and control group (SF < 200 ng/ml). Differences between the incidence of major adverse cerebral cardiovascular events (MACCE), carotid atherosclerotic plaques, and survival rate were analyzed.*

Results*: In one-year follow-up, there were no significant differences (p > 0.05) in the incidence of atherosclerotic plaques, MACCE and survival rate between the two groups. However, in a 3-year follow-up, there was significant difference (p < 0.05) in atherosclerotic plaques between the two groups, but the differences in MACCE and survival rate were not significant (p > 0.05). In a follow-up spanning 5 years, there were significant differences (p < 0.05) between atherosclerotic plaques and MACCE.*

Conclusions*: High serum ferritin level and iron overload have a positive association with PCAD in middle-aged male patients.*

Keywords*: Atherosclerosis, Coronary artery disease, Serum ferritin, Iron overload, Follow-up.*

DOI: 10.19193/0393-6384_2018_6_310

Received *March 30, 2018;* ***Accepted*** *June 20, 2018*

Introduction

Coronary artery disease (CAD) is a serious public health problem worldwide and it is the leading cause of death in many countries[1]. The disease is caused by atherosclerotic plaque formation within the inner walls of the heart arteries, which leads to myocardial ischemia. Dyslipidemia, smoking, hypertension, obesity, and family history are some of the risk factors that predispose to CAD. Some investigators have speculated that body iron status is positively associated with CAD[2-4], while others are of a contrary opinion, suggesting that body iron status has negative or no direct correlation with CAD[5, 6]. These disagreements may be due to several reasons. It might be due to difficulty in adjusting confounding factors such as race, sex, age, chronic diseases, and other significant risk factors which affect morbidity and prognosis of CAD. Secondly, the use of different sortation and measures of iron metabolism may be a factor[7]. In addition, the follow-up period used was brief (majority of the studies reported less than ten years follow-up).

Premature coronary artery disease (PCAD) is defined as CAD in males under 55 years, and in females under 65 years of age[8]. The aim of this study was to investigate the correlation between serum ferritin level and clinical outcomes of middle-aged male patients with PCAD.

Methods

Patients

A total of 420 middle-aged male patients with PCAD were recruited with case-control method for this study. Their ages ranged from 30 to 40 years.

The diagnostic criteria for CAD followed those of the World Health Organization (WHO)[9]. Patients were subjected to in-person interviews and questions bothering on their health habits, health status, smoking history, conditions of chronic diseases, and hospitalization history were asked. The patients' detailed characteristics such as educational status, CAD family history, dietary iron intake, red meat consumption, alcohol consumption, tobacco consumption, physical activity, diabetes history, obesity, hypertension, hyperuricemia, dyslipidemia, and anemia were subjected to clinical evaluation and case-match.

Biochemical indices such as total cholesterol (TC), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), fibrinogen, hemoglobin, and serum ferritin concentrations were also evaluated. Patients with significant risk factors for CAD were excluded, including those who were on coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), and iron-fortified foods. Obese patients, and those with family history of CAD, hypertension, dyslipidemia, hyperuricemia, atherosclerotic plaque, alcohol and tobacco addiction, or any other serious diseases were also excluded. Written informed consent was obtained from the patients before the start of the study.

Study variables

Educational level was calculated by the number of years spent in acquiring education. Smoking was defined as using five cigarettes daily for about 5 years, while drinking history was defined as consuming at least 100 g alcohol for 1 year. Obesity was defined as body mass index (BMI) ≥ 31 kg/m2 (for males)[10], while family history of CAD was defined as having immediate relatives (male under 55 years, and female under 65 years) who had suffered from CAD or myocardial infarction. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg obtained twice. Diabetes referred to fasting venous blood glucose level ≥ 7.0 mmol/L and/or ≥ 11.1 mmol/L 2 h after meal, while hyperuricemia was defined as uric acid concentration ≥ 380 μmol/L.[11].

Dyslipidemia was defined as TC level ≥ 5.18 mmol/L, according to the Chinese guidelines on prevention and treatment of dyslipidemia in adults, or LDL-C concentration ≥ 3.37 mmol/L, or TG concentration ≥ 1.7 mmol/L, or HDL-C level < 1.04 mmol/L. The concentrations of HDL-C, LDL-C, TC, and TG were determined in fasting venous blood specimens. Immune turbidimetric method was used for the determination of serum SF level, and SF ≥ 200 ng/ml was considered iron overload[12, 13]. Based on a cut off value of SF ≥ 200 ng/ml, the patients were classified into overload group (iron overload, SF ≥ 200 ng/ml) and control group (normal iron load, SF < 200 ng/ml). Dietary iron intake was estimated using the calculated food composition table according to Chinese Nutrition Society, which is based on the mean intakes for at least six months.

High-resolution ultrasonography was carried out using Philips ultrasonic system with a 7.5 MHz transducer. The atherosclerotic feature was investigated at the right and left common carotid and internal carotid arteries. Atherosclerotic feature was defined as a distinct zone with a focal atherosclerotic plaque, calcified deposits, thickening or protrusion into the lumen of the vessel, while focal thickening was defined as a mass with thickness >1.5 mm, or maximum intima-media thickness (IMT) >1.2 mm from any angle[14, 15].

Follow-up

The study plan incorporated a 5-year follow-up during which data were recorded and analyzed. The incidence of MACCE and carotid atherosclerotic plaques were collected and subjected to comparative analysis. The MACCE included death, non-fatal myocardial infarction, non-fatal stroke, re-vascularization, and re-hospitalization. The follow-up started immediately after discharge from hospital, while death dates were obtained from proxy, and other sources. The incidence of atherosclerotic plaques, MACCE and survival between the iron overload group and the control were compared at 1, 3, and 5 years, respectively.

Statistical analysis

Continuous variables are expressed as mean ± SD, while enumeration data are expressed as percentages (%). The data were analyzed using SPSS (Version 19.0), while differences between the two groups were compared using paired t-test and chi-square tests. Survival was calculated using Kaplan-Meier method and log-rank test. Values of $p < 0.05$ were considered statistically significant.

Results

Evaluation of study variables

There were no significant differences (p > 0.05) in the baseline data between the two groups, except for triacylglycerol and LDL-C concentrations, as shown in Table 1.

Characteristics	Overload group (n = 210)	Control group (n = 210)	*χ2 or t*	*p*
Age (years)	35.51 ± 4.36	34.79 ± 5.21	1.536	0.168
Smoking history				
Past smoker	71 (33.81 %)	58 (27.62 %)	1.891	0.169
Never smoked	139 (66.19 %)	152 (72.38 %)		
Drinking history				
Past drinker	97 (46.19 %)	89 (42.38 %)	0.618	0.432
Never drank	113 (53.81 %)	121 (57.62 %)		
Physical activity				
< 30min/day	142 (67.62 %)	134 (63.81 %)	0.676	0.411
≥ 30min/day	68 (32.38 %)	76 (36.19 %)		
Education				
Less than high school	110 (52.38 %)	101 (48.10 %)	0.771	0.380
High school and above	100 (47.62 %)	109 (51.90 %)		
BMI (kg/m2)	26.35 ± 2.68	25.87 ± 2.16	2.021	0.083
SBP (mmHg)	135.62 ± 16.57	137.76 ± 15.64	1.361	0.174
DBP (mmHg)	86.48 ± 15.39	84.88 ± 15.24	1.071	0.285
Total cholesterol (mmol/L)	5.01 ± 0.89	4.88 ± 0.76	1.61	0.152
Triacylglycerol (mmol/L)	1.36 ± 0.42	1.28 ± 0.41	1.975	0.049
HDL-C (mmol/L)	1.31 ± 0.30	1.35 ± 0.26	1.46	0.188
LDL-C (mmol/L)	2.70 ± 0.31	2.76 ± 0.30	2.016	0.044
Fibrinogen (g/L)	3.08 ± 0.54	2.96 ± 0.66	2.039	0.081
Hemoglobin (g/L)	133.61 ± 12.15	132.02 ± 13.47	1.27	0.205
Uric acid (UA) (μmol/L)	223.77 ± 43.58	217.66 ± 46.14	1.395	0.164
Iron intake (mg/day)	18.22 ± 4.12	17.66 ± 3.41	1.505	0.176
Clinical presentation				
Stable angina	93 (44.29 %)	106 (50.48 %)	2.059	0.357
Unstable angina	66 (31.43 %)	54 (25.71 %)		
Acute myocardial infarction	51 (24.33 %)	50 (23.81 %)		

Table 1: Comparison of baseline data between the two groups.

Clinical outcome with 1 year follow-up

In one-year follow-up, 5 cases (2.38%) dropped out in iron overload group, while 4 (1.90%) dropped out in the control. In the control group, 20 cases suffered from MACCE, while 6 died of CAD in the overload group. A total of 30 cases were re-hospitalized for MACCE, including 10 cases who died of CAD. As for atherosclerotic plaques of common carotid and internal carotid arteries, 24 cases were recorded in control group, while 29 cases were seen in the iron overload group. There were no significant differences (p > 0.05) in the incidence of atherosclerotic plaques, MACCE and survival rate between the two groups. These results are shown in Table 2.

Group	Number of cases	Atherosclerosis	MACCE	Survival rate
Control group (< 200 μg/L)	210	24 (11.43%)	20 (9.52%)	97.14%
Overload group (≥200 μg/L)	210	29 (13.81%)	30 (14.15%)	95.24%
χ2		0.54	2.27	1.04
p		0.463	0.132	0.308

Table 2: Comparison of clinical outcome with one-year follow-up between the two groups.

Clinical outcome with 3 years follow-up

In three years, a total of 9 cases (4.29%) were dropped out in iron overload group and 10 (4.76%) in the control. In the control group, 37 cases suffered from MACCE, including 18 cases who died of CAD, while in the iron overload group, 54 cases were rehospitalized for MACCE, including 25 cases who died of CAD. A total of 56 cases with carotid atherosclerotic plaques were recorded in the control group and 76 in iron overload group. There was a significant difference (p < 0.05) in the incidence of atherosclerotic plaques between the two groups, while there was no significant difference (p > 0.05) between MACCE and survival rate. The results are shown in Table 3.

Group	Number of cases	Atherosclerosis	MACCE	Survival rate
Control group (< 200 μg/L)	210	56 (26.67%)	37 (17.62%)	91.43%
Overload group (≥ 200 μg/L)	210	76 (36.19%)	54 (25.71%)	88.10%
χ2		4.419	4.054	1.27
p		0.036	0.044	0.26

Table 3: Comparison of clinical outcome with 3 years follow-up between the two groups.

Clinical outcome with 5 years follow-up

In five years, 14 cases (6.67%) dropped out in iron overload group, while 16 (7.62%) cases dropped out in the control group. In the control group, 57 cases suffered from MACCE, including

26 cases who died of CAD, while in the iron overload group, 85 cases were re-hospitalized for MACCE, including 41 cases who died of CAD. A total of 76 cases with carotid atherosclerotic plaques were recorded in the control group, while 96 cases were seen in iron overload group. There were significant differences ($p < 0.05$) between atherosclerotic plaques, MACCE and survival rate. These results are shown in Table 4.

Group	Number of cases	Atherosclerosis	MACCE	Survival rate
Control group (< 200 μg/L)	210	76 (36.19 %)	57 (27.14 %)	87.62%
Overload group (≥ 200 μg/L)	210	96 (45.71 %)	85 (40.48 %)	80.48%
χ^2		3.938	8.341	3.996
P		0.047	0.004	0.046

Table 4: Comparison of clinical outcome with 5 years follow-up in the two groups.

Discussion

In the present study, there were significant differences in carotid atherosclerotic plaques from 3 to 5 years between the two groups, while there were no significant differences in one-year follow-up. In addition, there were significant differences in the incidence of MACCE and survival rate in 5 years follow-up between the two groups, while there were no significant differences in one-year and 3 years follow-up, respectively. The results appear to suggest that serum ferritin level and iron status were correlated to PCAD, and that there was a positive correlation between iron overload and PCAD.

"Iron hypothesis" which was postulated more than twenty years ago, does not support a strongly positive or negative correlation between body iron status and CAD[16, 17]. Thus, the results obtained in this are not in agreement with iron hypothesis. The deviation may be due to characteristics such as race, age, sex, health status, physical activity and various risk factors. It is difficult to speculate that the rigorous exposure model led to CAD, because it can confound the association between body iron status and CAD[18, 19].

In order to minimize and control these confounding factors, this study had several unique strengths which included the exclusion of patients with obesity, CAD family history, hypertension, hyperuricemia, dyslipidemia, current tobacco and alcohol addiction. In addition, dietary iron intake and body iron status were taken into consideration in follow-up, since body iron stores and functional iron are correlated to sex and age. Due to the regular menstrual iron depletion in women[20], participants only consisted of male patients. Since body iron stores tend to increase with advancing age[21, 22], only middle-aged men within the range of 30 to 40 years were used.

Several studies have attempted to explain the mechanism of "iron hypothesis". In those studies serum ferritin was considered to be the high-sensitive indicator for assessing body iron overload. Serum ferritin is correlated with catalytic iron and oxidative damage, which can lead to damage to endothelial cells and human atherosclerotic plaques[23, 24, 25]. Iron overload increases lipid peroxidation and blood viscosity, thereby increasing susceptibility to myocardial ischemia[26, 27, 28].

In contrast, low levels of iron may reduce oxidative stress[29].

Study limitations

In this study, some of the limitations included the use of serum ferritin as the sole indicator for body iron status. Total iron-binding capacity (TIBC), storage iron, saturation of transferrin and serum transferrin were not measured. Since bone-marrow biopsies for the determination of body iron status were hard to conduct in follow-up, serum ferritin level was used as the indicator for body iron status in this study[30, 31]. Angiography and intravascular ultrasound are considered as "golden standard" for detection of atherosclerotic plaques[32, 33]. However, these could not be used for all the patients. The use of carotid ultrasound for detection of atherosclerotic plaques would affect the accuracy of results. Only a single race was used for this study. Therefore, further studies should be developed in other populations.

Conclusion

High serum ferritin level and iron overload have are positively associated with PCAD in middle-aged male patients.

References

1) Pollock A, Jones DS. Coronary artery disease and the contours of pharmaceuticalization. Soc Sci Med 2015; 131: 221-227.
2) Pourmoghaddas A, Sanei H, Garakyaraghi M, Esteki-Ghashghaei F, Gharaati M. The relation between body iron store and ferritin, and coronary artery disease. ARYA Atheroscler 2014; 10: 32-36.
3) Gill D, Del-Greco MF, Walker AP, Srai SKS, Laffan MA, et al. The effect of iron status on risk of coronary artery disease: a mendelian randomization study-brief report. Arterioscler Thromb Vasc Biol 2017; 37: 1788-1792.
4) Iqbal MP, Mehboobali N, Tareen AK, Yakub M, Iqbal SP, et al. Association of body iron status with the risk of premature acute myocardial infarction in a Pakistani population. PLoS One 2013; 8: 67981.
5) Zhou Y, Liu T, Kang P, Jia C. Association of better iron status biomarkers and coronary artery disease risk. Intern Med J 2014; 44: 846-850.
6) Grammer TB, Kleber ME, Silbernagel G, Pilz S, Scharnagl H, et al. Hemoglobin, iron metabolism and angiographic coronary artery disease (The Ludwigshafen Risk and Cardiovascular Health Study). Atherosclerosis 2014; 236: 292-300.
7) Pilote L, Joseph L, Bélisle P, Robinson K, Van Lente F, et al. Iron stores and coronary artery disease: a clinical application of a method to incorporate measurement error of the exposure in a logistic regression model. J Clin Epidemiol 2000; 53: 809-816.
8) Catalin T, Cameron H, John GBM, Bruce F, Jiri F. Coronary artery calcium findings in asymptomatic subjects with family history of premature coronary artery disease. BMC Cardiovasc Disord 2012; 12:1-7.
9) Jankovic N, Geelen A, Streppel MT, Groot de LC, Jong JCK, et al. WHO guidelines for a healthy diet and mortality from cardiovascular disease in European and American elderly: the CHANCES project. Am J Clin Nutr 2015; 102: 745-756.
10) Howe LD, Zimmermann E, Weiss R, Sørensen TI. Do rapid BMI growth in childhood and early-onset obesity offer cardiometabolic protection to obese adults in mid-life? Analysis of a longitudinal cohort study of Danish men. BMJ Open 2014; 4: 004827.
11) Zhao SP. Amendment of the low-density lipoprotein cholesterol target in the 'Chinese Guidelines for the Prevention and Treatment of Adult Dyslipidemia': Opinion. Chronic Dis Transl Med 2016; 2: 7-9.
12) Baharvand M, Manifar S, Akkafan R, Mortazavi H, Sabour S. Serum levels of ferritin, copper, and zinc in patients with oral cancer. Biomed J 2014; 37: 331-336.
13) Cippà PE, Boucsein I, Adams H, Krayenbuehl PA. Estimating iron overload in patients with suspected liver disease and elevated serum ferritin. Am J Med 2014; 127: 1-3.
14) Novo S, Corrado E, Novo G, Dell'Oglio S. Association of carotid atherosclerosis with coronary artery disease: comparison between carotid ultrasonography and coronary angiography in patients with chest pain. G Ital Cardiol 2012; 13: 118-123.
15) Polak JF, O'Leary DH. Edge-detected common carotid artery intima-media thickness and incident coronary heart disease in the multi-ethnic study of atherosclerosis. J Am Heart Assoc 2015; 4: 001492.
16) Zhou Y, Liu T, Tian C, Kang P, Jia C. Association of serum ferritin with coronary artery disease. Clin Biochem 2012; 45: 1336-1341.
17) Aursulesei V, Cozma A, Krasniqi A. Iron hypothesis of cardiovascular disease: still controversial. Rev Med Chir Soc Med Nat Iasi 2014; 118: 901-909.
18) Erdal M, Aparcı M, Işılak Z, Bozlar U, Arslan Z, et al. Clinical features of aviators with coronary artery disease diagnosed by multislice CT angiography. Anadolu Kardiyol Derg 2014; 14: 150-154.
19) Inci MF, Özkan F, Ark B, Vurdem ÜE, Ege MR, et al. Sonographic evaluation for predicting the presence and severity of coronary artery disease. Ultrasound Q 2013; 29: 125-130.
20) Moschonis G, Papandreou D, Mavrogianni C, Giannopoulou A, Damianidi L, et al. Association of iron depletion with menstruation and dietary intake indices in pubertal girls: the healthy growth study. Biomed Res Int 2013; 2013: 423263-423271.
21) DePalma RG, Zacharski LR, Chow BK, Shamayeva G, Hayes VW. Reduction of iron stores and clinical outcomes in peripheral arterial disease: outcome comparisons in smokers and non-smokers. Vascular 2013; 21: 233-241.
22) Kim TH, Hwang HJ, Kim SH. Relationship between serum ferritin levels and sarcopenia in Korean females aged 60 years and older using the fourth Korea National Health and Nutrition Examination Survey (KNHANES IV-2, 3), 2008-2009. PLoS One 2014; 9: 90105.
23) Lapenna D, Ciofani G, Pierdomenico SD, Giamberardino MA, Ucchino S, et al. Association of serum bilirubin with oxidant damage of human atherosclerotic plaques and the severity of atherosclerosis. Clin Exp Med 2018; 18: 119-124.
24) Rajapurkar MM, Shah SV, Lele SS, Hegde U, Lensing S, et al. Association of catalytic iron with cardiovascular disease. Am J Cardiol 2012; 109: 438-442.
25) Ma H, Lin H, Hu Y, Li X, He W, et al. Serum ferritin levels are associated with carotid atherosclerosis in Chinese postmenopausal women: the Shanghai Changfeng Study. Br J Nutr 2015; 114: 1064-1071.
26) Jankowska EA, Wojtas K, Kasztura M, Mazur G, Butrym A, et al. Bone marrow iron depletion is common in patients with coronary artery disease. Int J Cardiol 2015; 182: 517-522.
27) Hung MY, Hsu KH, Hu WS, Chang NC, HY, et al. Gender-specific prognosis and risk impact of C-reactive protein, hemoglobin and platelet in the development of coronary spasm. Int J Med Sci 2013; 10: 255-264.
28) Aranda N, Fernandez-Cao JC, Tous M, Arija V. Increased iron levels and lipid peroxidation in a Mediterranean population of Spain. Eur J Clin Invest 2016; 46: 520-526.
29) Berdoukas V, Coates TD, Cabantchik ZI. Iron and oxidative stress in cardiomyopathy in thalassemia. Free Radic Biol Med 2015; 88:3-9.
30) McSorley ST, Jones I,[McMillan DC, Talwar D. Quantitative data on the magnitude of the systemic inflammatory response and its relationship with serum measures of iron status. Transl Res 2016; 176: 119-126.
31) Schreiner F, Krayenbühl PA, Goede J, Nowak A.

Approach to the Patient with Elevated Serum Ferritin. Praxis (Bern 1994) 2016; 105: 543-551.
32) Veselova TN, Shabanova MS, Mironov VM, Merkulova IN, Ternovoy SK. Computed tomography in the evaluation of coronary atherosclerotic plaques: comparison with intravascular ultrasound. Kardiologiia 2017; 1: 42-47.
33) Park HB, Lee BK, Shin SH, Heo R, Arsanjani R, et al. Clinical feasibility of 3D automated coronary atherosclerotic plaque quantification algorithm on coronary computed tomography angiography: comparison with intravascular ultrasound. Eur Radiol 2015; 25: 3073-3083.

Corresponding author
XIAOXIAO CHANG
Email: zo1269@163.com
(China)