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The relationship between fetuin-A and coronary atherosclerotic heart disease (CHD) and CHD-related risk factors

A retrospective study

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Abstract

Fetuin-A plays an important role in antivascular calcification and inflammatory response, it is necessary to explore the relationship between fetuin-A and coronary atherosclerotic heart disease (CHD) and CHD-related risk factors.

A total of 92 patients with CHD as the research group, and 60 healthy persons as the control group were enrolled from May 2019 to May 2020. Fetuin-A levels were determined by enzyme-linked immunosorbent assay, and the characteristics and clinical data were collected and compared. Logistic regression was used to analyze the factors influencing CHD.

The age, proportion of males, patients with hypertension and diabetes, as well as fetuin-A level in the research group were significantly higher than those in the control group, but the high-density lipoprotein cholesterol level was significantly lower than that in the control group ($P < .05$). Logistic regression analysis and correction showed that gender, age, blood pressure, and diabetes were related to the onset of CHD, and there was a significant correlation between the level of fetuin-A and age ($P < .05$).

Serum fetuin-A was related to the onset risk of CHD, and showed a significant correlation with age.

Abbreviations: CHD = coronary atherosclerotic heart disease, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride.

Keywords: coronary atherosclerotic heart disease, fetuin-A, risk factors

1. Introduction

Coronary atherosclerotic heart disease (CHD) is a kind of heart disease caused by coronary atherosclerotic lesions, which leads to stenosis or blockage of vascular lumen, myocardial ischemia, hypoxia or necrosis.[1] However, the scope of CHD may be wider, including inflammation, embolization, etc which causes stenosis or occlusion of the lumen. The World Health Organization classifies CHD into 5 categories: asymptomatic myocardial ischemia (recessive CHD), angina, myocardial infarction, ischemic heart failure (ischemic heart disease), and sudden cardiac death.[2] It is usually divided into the stable CHD and acute coronary syndrome. According to the report, the prevalence of cardiovascular diseases in China has continued to rise. At present, the total number of patients has reached 290 million, including 270 million with hypertension, 13 million with stroke, 11 million with coronary heart disease, 5 million with pulmonary heart disease, 4.5 million with heart failure, 2.5 million with rheumatic heart disease and 2 million with congenital heart disease.[3,4] CHD is the leading cause of death in the United States and many developed countries. However, the mortality of CHD had been declining in the United States since the 1960s. In 2015, the mortality rate of cardiovascular disease in urban residents was 264.84/100,000, including 136.61/100,000 for heart disease and 128.23/100,000 for cerebrovascular disease. The data of rural areas were 298.42/100,000, 144.79/100,000 and 153.63/100,000, which were higher than those of cities.[5]

Fetuin-A is known as α-Heremans–Schmid glycoprotein, which is synthesized and secreted by liver and widely exists in extracellular fluid. It mainly plays a role in regulation of osseous and vascular calcification by transient formation of soluble colloidal spheres containing fetuin-A, calcium, and phosphate, which are able to prevent hydroxyapatite crystallization and abnormal calcification in cell tissues.[6,7] Hence, its main function is thought as an inhibitor of arterial calcification. Moreover, fetuin-A can bind the insulin receptor tyrosine kinase in peripheral tissues, thereby inhibiting the insulin- induced

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JZ and MH contributed equally to this study.

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intracellular signal cascade.[8,9] Theoretically, the effects of fetuin-A are closely related to the occurrence and development of CHD. In recent years, more and more scholars at home and abroad have studied the relationship between fetuin-A and CHD. However, there are currently significant differences in the clinical study results regarding the correlation between serum fetuin-A level and the risk of CHD. The higher fetuin-A levels were only associated with lower risk of CHD among women with high C-reactive protein levels.[10] While the EPIC-Potsdam Study, a large prospective case cohort study, suggested that high fetuin-A level was closely related to acute myocardial infarction and stroke, and proposed that fetuin-A was involved in the pathogenesis of cardiovascular disease.[11]

As previously mentioned, the association of fetuin-A with CHD has not been well studied in general population samples, and the existing researches reached no unanimous conclusions. Therefore, the purpose of this study was to discuss the correlation between fetuin-A and CHD, as well as CHD-related risk factors, hoping to provide a reference for the related future studies.

2. Materials and methods

2.1. Clinical data

A total of 92 patients diagnosed with CHD were admitted and treated in our hospital from May 2019 to May 2020, and served as the research group. The diagnostic criteria was referenced to the related contents of *Diagnostic Criteria for Cardiovascular Internal Diseases*.[5] Another 60 healthy persons after physical examination in our hospital during the same period were selected as the control group. The patients in the research group included 69 males and 23 females, aged 43~87 years, with an average age of (62.35 ± 8.59) years, while the control group included 28 males and 32 females, aged 41~85 years, with an average age of (61.36 ± 9.15) years. The informed consent for the patients and their family members to participate in this study was obtained, which was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the Ethics Committee of our hospital.

Inclusion criteria: patients were diagnosed with CHD in the research group; and patients with complete clinical data.

Exclusion criteria: patients with severe cardiac insufficiency or primary cardiomyopathy; acute attack with severe infection or chronic inflammatory disease; and liver and kidney dysfunction or long-term use of hormones.

2.2. Methods

The routine biochemical serum tests were performed on 2 groups, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). The Hitachi 760020 automatic biochemical analyzer was used to detect the serum level of fetuin-A. The enzyme-linked immunosorbent assay kit was purchased from Shanghai Xitang Biotechnology Co., Ltd., and the operation was in strict accordance with the instructions. The mean value was taken from all the results in 3 repetitions.

2.3. Observation index

The general information of the patients was collected, including gender, age, smoking history, history of hypertension and diabetes, etc. The routine biochemical serum tests were performed on 2 groups, including TC, TG, HDL-C, and LDL-C. Fetuin-A levels of both groups were determined by enzyme-linked immunosorbent assay, and logistic regression was used to analyze and correct the pathogenic factors of CHD and the differences between both groups.

2.4. Statistical analysis

The qualitative data such as gender, medical history, symptoms, etc were represented as the frequency distribution and percentage, and the comparison between groups was analysed by chi-square test. The Shapiro Wilk test was used to assess data normality on continuous variables. The quantitative data with normal distribution were represented as mean ± standard deviation, and the comparison between the 2 groups was analysed by *t* test. The correlation between fetuin-A and CHD was analyzed by multiple regression, and binary logistic regression analysis was used to assess fetuin-A and the risk factors of CHD. SPSS 22.0 statistical software (IBM, New York, NY, USA) was used for analysis, and it ($P < .05$) indicated that the difference was statistically significant.

3. Results

3.1. Clinical data

The Figure 1 demonstrated the flow graph illustrating study process. The general information of the patients was collected, including gender, age, smoking history, history of hypertension and diabetes, etc. The comparison of general information showed that the age in the research group was significantly higher than that in the control group, the proportion of males in the research group was significantly higher, and more patients suffered from hypertension and diabetes ($P < .05$). The HDL-C level in the research group was significantly lower than that in the control group ($P < .05$). There were no statistically significant differences in smoking history, TC, TG, and LDL-C between the 2 groups ($P > .05$), as shown in Table 1.

3.2. Correlation between fetuin-A level and onset of CHD

The fetuin-A level of the patients in research group was 421.36 ± 101.13 g/L, significantly higher than that in the control group of 278.52 ± 137.15 g/L ($P < .05$). The logistic regression analysis and correction showed that gender, age, blood pressure, and diabetes were related to the onset of CHD, as shown in Table 2.

3.3. Correlation between fetuin-A level and risk factors of CHD

The logistic regression analysis showed no significant correlation between fetuin-A level and gender, blood pressure, diabetes, TC, TG, HDL-C or LDL-C ($P > .05$), while there was a significant correlation between the level of fetuin-A and age ($P < .05$), as shown in Table 3.

4. Discussion

CHD is a serious disease that seriously endangers human health and quality of life, and it is commonly known as acute coronary syndrome[12] together with acute myocardial infarction. CHD is mostly caused by corrosion or sudden rupture of atherosclerotic

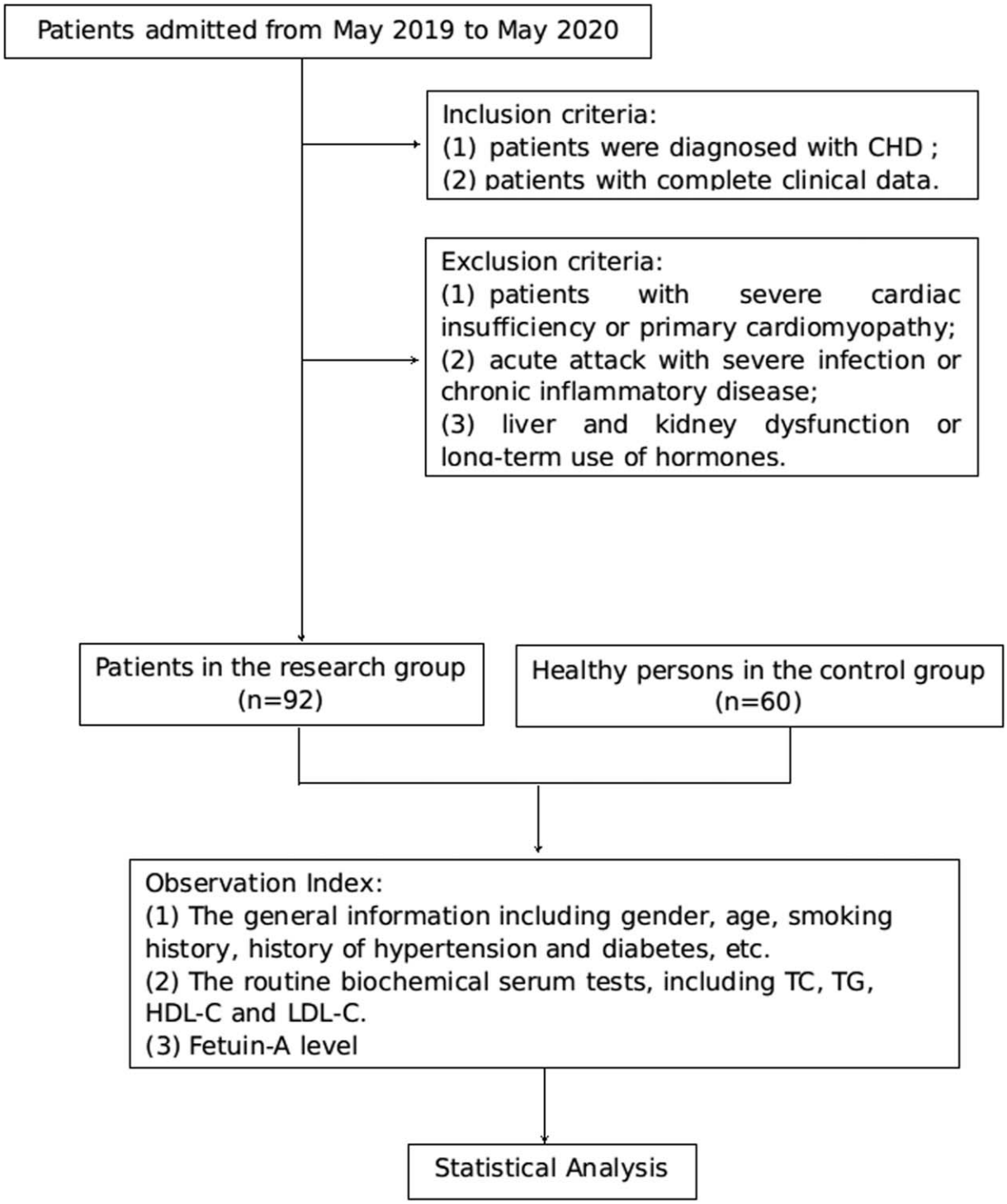

Figure 1. Flow graph illustrating study process.

unstable plaques on the surface of coronary arteries, which then leads to thrombosis and causes severe narrowing of the coronary artery lumen. Inflammatory factors play a key role in this process.[13–15]

At present, the traditional causes of CHD include: gender, age, smoking history, hypertension, hyperlipidemia, diabetes, etc. In recent years, it has been found that fetuin-A may also be involved.[7]

The comparison of general information showed that the proportions of males, elders and patients with hypertension, diabetes as well as higher HDL-C level in the research group were higher than those in the control group ($P < .05$), but there were no statistically significant differences in smoking history, TC, TG, and LDL-C between the 2 groups ($P > .05$). In the study of Song et al,[16] the mean age, serum TC, LDL-C in the CHD group were higher than in the non-CHD group, and the numbers of patients

Table 1

Comparison of clinical data.

Item	Research group (n = 92)	Control group (n = 60)	t/x^2	P
Age	62.35 ± 8.59	54.36 ± 9.15	5.463	.000
Male	69 (75.00)	28 (46.77)	16.732	.000
Female	23 (25.00)	32 (53.33)		
Smoking history	20 (21.74)	8 (13.33)	2.446	.118
Hypertension	63 (68.48)	15 (25.00)	37.972	.000
Diabetes	18 (19.56)	1 (1.67)	16.866	.000
TC (mmol/L)	4.85 ± 1.13	4.71 ± 0.85	0.820	.414
TG (mmol/L)	2.14 ± 1.41	1.82 ± 0.76	1.611	.109
HDL-C (mmol/L)	1.03 ± 0.21	1.15 ± 0.25	3.192	.002
LDL-C (mmol/L)	2.94 ± 0.91	2.85 ± 0.72	0.645	.520

HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride.

with type 2 diabetes mellitus, hypertension, and a history of smoking in the CHD group were also higher than those in the non-CHD group. Huth et al[17] indicated that the cases of CHD comprised more men than women, they were more likely to be physically inactive, to suffer from actual hypertension and to be current or former smokers. In the view of gender, age, history of hypertension and diabetes, our results were consistent with other studies, but the results of smoking history, serum TC and LDL-C, which probably was caused by different inclusion criteria of patient, and a larger sample size and a more uniform criteria may be needed to address this issue definitively.

Fetuin-A plays an important role in antivascular calcification and inflammatory response, and in theory, the effects of fetuin-A are closely related to the occurrence and development of CHD. Altinisik et al[18] reported that fetuin-A was negatively correlated with the severity of coronary calcification.[19] Some studies, however, have mixed results. Nababan et al[20] found that serum fetuin-A level in the CHD group was significantly lower than that in the non-CHD group; Gonzalez-Cabrera et al[21] reported that patients with acute coronary syndrome with low fetuin-A level and high levels of C-reactive protein had higher mortality. Sari et al[22] believed that serum fetuin-A level was significantly correlated with hypertriglyceride, but could not be used as a predictive factor for future cardiovascular disease risk in patients with severe atherosclerosis. Therefore, nowadays the exact relationship between serum fetuin-A level and the risk of atherosclerotic disease, especially CHD, remains unclear.[23] In our study, the fetuin-A level of the patients in research group was significant higher than that in the control group ($P < .05$), corresponding to some studies mentioned. The Logistic Regression analysis indicated that fetuin-A level showed a significant correlation with age ($P < .05$). The reason for this result may be

Table 2

Comparison of correlation between fetuin-A level and onset risks of CHD.

Group	Cases	Fetuin-A (g/L)	P	Analysis upon multi-factor Survey	
				P	OR (95% CI)
Research group	92	421.36 ± 101.13	.839	.001	5.324~(2.089~16.056)
Control group	60	279.03 ± 136.11			

CHD = coronary atherosclerotic heart disease.

Table 3

Correlation between fetuin-A level and risk factors of CHD.

Influence factor	B	t	P
Age	0.205	2.458	.032
Gender	0.052	−0.535	.515
Smoking history	0.113	1.409	.184
Hypertension	0.025	0.242	.921
Diabetes	0.025	0.138	.821
TC	−0.068	−0.448	.697
TG	0.105	1.102	.236
HDL-C	0.017	0.257	.828
LDL-C	0.128	0.748	.471

CHD = coronary atherosclerotic heart disease, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride.

that the function of liver organs decreases with age, which leads to the increase of secretion of fetuin-A. Therefore, elderly patients are more likely to have CHD.

In conclusion, serum fetuin-A was related to the onset risk of CHD and advanced age may be a risk factor of CHD.

Author contributions

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