Study on the Predictive Effect of Fibrinogen on Vascular Calcification

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Abstract

Background: The levels of fibrinogen (FIB), lipoprotein and high-density lipoprotein (HDL) are related to vascular calcification (VC), but their predictive ability for VC has not been reported.

Aims: The purpose of this study was to evaluate the predictive efficacy of FIB, lipoprotein and HDL by retrospective analysis of FIB, lipoprotein and HDL levels in patients with VC.

Methods: We collected the relevant indicators of 462 patients admitted to the Department of Vascular Surgery of the First Hospital of Hebei Medical University from August 2018 to July 2020, including 189 patients with vascular calcification (40.9%) and 273 patients without vascular calcification (59.1%). 75% of the collected data is used for modeling (modeling group) and 25% for verification (verification group). Univariate analysis and multivariate analysis were used to evaluate the effects of FIB, lipoprotein and HDL on VC, and the predictive model ROC curve was used to evaluate its predictive efficiency.

Results: The results of multivariate analysis showed that FIB, lipoprotein and HDL were independent predictors of VC. Then the models of the three factors are established respectively. The area under the ROC curve of the prediction model of FIB, lipoprotein and HDL was 0.8018, 0.7348 and 0.7019, respectively.

Conclusions: Fibrinogen has a better predictive ability than high-density lipoprotein and lipoprotein in patients with arteriosclerosis.

1. Introduction

Vascular calcification (VC) is a very common disease, and the prevalence rate of calcification increases with age. Relevant statistics show that VC exists in $\geq 90\%$ of men and $\geq 67\%$ of women over the age of 70 [1]. VC is not only an important cause of increased morbidity and mortality of cardiovascular disease but also a widespread pathological phenomenon harmful to the health of the middle-aged and elderly. VC is a marker of atherosclerosis and an independent predictor of cardiovascular events. It is closely related to all-cause mortality and has always been an important field of cardiovascular medical research [1–4].

Fibrinogen is a glycoprotein of 340kd, which consists of three different pairs of polypeptide chains a, b and g. It is mainly synthesized by hepatocytes in the liver and can be degraded by fibrinolytic enzymes to form fibrinogen degradation products. Lipoprotein is a kind of hydrophobic core rich in sterolipid and triglyceride and spherical particles composed of protein, phospholipid, cholesterol, and so on. Lipoproteins play an important role in the packaging, storage, transport and metabolism of extracellular lipids. High-density lipoprotein (HDL) is a complex lipoprotein composed of lipids and proteins and their regulatory factors, mainly produced by the liver and small intestine. Current studies have shown that serum inflammatory markers are significantly correlated with VC [5], but the predictive efficiency of FIB in VC has not been reported. Although previous studies have shown that there is a correlation between

lipoprotein and HDL and VC, its ability to predict VC has not been reported. Therefore, the purpose of this study is to further evaluate the predictive ability of FIB, lipoprotein and HDL to VC.

2. Patients

This study was approved by the Ethics Committee of the First Hospital of Hebei Medical University (ethics code is 20200617). We collected the relevant indicators of 462 patients admitted to the Department of Vascular Surgery of the First Hospital of Hebei Medical University from August 2018 to July 2020, including 189 patients with vascular calcification (40.9%) and 273 patients without vascular calcification (59.1%). Abdominal aortic calcification score described by Kauppila et al. ^[6]. Lateral lumbar spine radiographs were obtained in the standing position to measure the severity of calcification in the aorta at the level of the first four lumbar vertebrae. The following scores were assigned for the presence of calcifications in the longitudinal aortic wall opposite each vertebra: 1, small calcified deposits occupying less than 1/3 of the aortic wall; 2, one-third or more but less than two-thirds of the wall of the aorta; and 3, calcification of two-thirds or more of the wall of the aorta. The anterior and posterior aortic walls were evaluated separately and the total was obtained to get a score out of 24 ^[7]. The abdominal aortic calcification score of 0 is the patient without vascular calcification, and the abdominal aortic calcification score > 0 is the patient of vascular calcification.

3. Methods

3.1. Data collection

We collected indicators of age, height, weight, fibrinogen, fibrinogen degradation products, triglycerides, cholesterol, HDL, low-density lipoprotein, lipoprotein, glutamyl transferase, and C-reactive protein from the database, and collected related indicators of vascular-free calcification for 273 patients for comparison.

3.2. Statistical analysis

All statistical analyses and random allocation were performed by Empower Stats and R project version 3.3.3 (<http://www.rproject.org/>). The measurement data that obey normal distribution are expressed by mean $\pm$ standard deviation, and the comparison between groups is expressed by independent sample t-test, count data use case (%), chi-square test or Fisher exact probability method. Univariate analysis and multivariate regression analysis were used to analyze the differences between groups by Kaplan-Meier method and Log-Rank method. The test level was $\alpha = 0.05$ ($p < 0.05$). The VC prediction ROC curve based on FIB, lipoprotein and low-density lipoprotein was established by Empower Stats.

4. Results

4.1 The population analysis is shown in Table 1.

4.2 All variables were analyzed by univariate analysis (Table 2). Result variable: vascular calcification. Exposure variables: neutrophil (NEUT), lymphocyte (LY), FIB (FIB), FIB degradation product (FDP), triglyceride (TG), total cholesterol (TC), HDL (HDL), low-density lipoprotein (LDL), lipoprotein (Lipoproteins), glutamyltransferase (GGT), C-reactive protein (CRP), adjustment variable: None. In univariate analysis, FIB, lipoprotein and HDL were significantly correlated with VC ($p < 0.05$). These significant correlation variables were used in the multivariate analysis (Table 3). The results of multivariate analysis showed that FIB, lipoprotein and HDL were independent predictors of VC ($p < 0.05$).

4.3 Analysis of the ROC curve of VC prediction model by FIB, lipoprotein and HDL

Univariate analysis and multivariate analysis showed that FIB, lipoprotein and HDL had effects on VC. To further detect and compare the predictive efficacy of these indexes on VC, the ROC curves of FIB, lipoprotein and HDL on VC prediction models were established (Fig. 1). The ROC curve analysis and optimal threshold analysis of FIB, lipoprotein and HDL to VC prediction model are shown in Table 4. The area under the ROC curve of FIB was 0.8018, and the area under the ROC curve of lipoprotein was 0.7348 and the area under the ROC curve of HDL was 0.7019. The models with ROC curves ranging from 0.70 to 0.80 are considered to be good, while the models with areas under the curves ranging from 0.80 to 0.90 have excellent resolution. The area under the ROC curve of the prediction model of FIB, lipoprotein and HDL was 0.8018, 0.7348 and 0.7019, respectively. Our research shows that lipoprotein and HDL are effective in predicting VC, and FIB is strong in predicting VC.

5. Discussion

Vascular calcification ((VC)) is a very common disease. VC is characterized by increased vascular wall stiffness and decreased compliance, which can lead to serious clinical adverse reactions, including systolic hypertension, left ventricular hypertrophy, coronary artery ischemia, congestive heart failure, and possible plaque rupture, thrombosis and myocardial infarction [8, 9]. Once considered to be a passive process, it is now recognized that VC is a complex and highly regulated process involving a series of mediating factors, including activation of cellular signaling pathways, circulatory calcification inhibitors, genetic factors and hormones. Different phenotypes may have different effects on plaque vulnerability and clinical outcomes [1, 4]. For example, histological studies have shown that coronary artery calcification is mainly limited to the intima, however, intima and media calcification can occur in large arteries, including aorta; media calcification is more closely related to aging, diabetes and severe nephropathy [10]. The structural characteristics of different vascular beds may also play a role. Because of its complex and multifaceted characteristics, there is no targeted treatment for VC at present.

The pathogenesis of intravascular calcification is not fully understood, but recent studies have shown that it is similar to neointimal calcification, which is considered to be a repeat of bone formation and ultimately depends on the nucleation and crystal growth of hydroxyapatite [1, 11]. Related studies have shown that inflammation, vesicle secretion, oxidative stress in apoptotic bodies and plaques, as well as

increased levels of VSMC and cholesterol, radiotoxicity and adipogenesis contribute to the progression of calcification [4].

VC is usually the result of errors in adaptive mechanisms. Inflammatory reaction and oxidative stress are important pathological processes of VC [12]. In general, chronic inflammation seems to be the central factor for abnormal soft tissue calcification, and the site of chronic inflammation in the vascular system has been proved to be the site of atherosclerotic calcification in mice [9]. There is strong evidence that inflammation plays an important, at least partially reversible, role in the development of VC, and inflammatory markers may be useful additional tools for assessing cardiovascular risk in clinical practice. The combined evaluation of VC and inflammatory markers can improve the non-invasive assessment of cardiovascular risk, so those high-risk patients can be selected for preventive treatment or more regular physical examination, and the possibility of de-targeting therapy for pro-inflammatory mechanism can be developed in the future [13]. As an important biomarker of systemic inflammation, FIB is a glycoprotein synthesized and secreted by hepatocytes. FIB is the main coagulation protein in plasma, the determinant of blood viscosity and the cofactor of platelet aggregation. The increase of plasma FIB concentration is an independent risk factor for cardiovascular disease [14, 15]. Our results also show that FIB has an effect on vascular calcification, which is consistent with previous studies.

According to related studies, lipoprotein can regulate the initiation of VC, which is an important determinant in the progression of VC [2,16–19]. Low-density lipoprotein is more likely to cause VC, especially, the elevated level of oxidized low-density lipoprotein is a risk factor for cardiovascular disease [20–22]. Our results are consistent with previous studies. But HDL (HDL) has the inhibitory ability to VC [4, 23]. As a controversial lipoprotein, the inhibitory effect of HDL on VC is mainly mediated by its role in cholesterol reverse transport [24], a biological process that promotes the transfer of free cholesterol from the arterial wall back to the liver for reuse or excretion into bile. HDL can inhibit the oxidation of low-density lipoprotein and its anti-inflammatory effect on cellular signals caused by oxidized low-density lipoprotein. HDL also inhibits macrophage Toll-like receptor 4-mediated inflammation, which is dependent on cholesterol efflux through ATP binding cassette A1 and transporter G1. Besides, HDL has an antidiabetic effect [25]. Our results also show that high-density lipoprotein negatively regulates vascular calcification, which is consistent with previous studies.

In this study, using univariate and multivariate analysis, we determined that FIB, lipoprotein and HDL were independent predictors of VC. The models with ROC curves ranging from 0.70 to 0.80 are considered to be good, while the models with areas under the curves ranging from 0.80 to 0.90 have excellent resolution. The ROC curve analysis of the prediction model established in our study shows that lipoprotein and HDL have good prediction efficiency for VC, and fibrinogen has better predictive ability than high-density lipoprotein and lipoprotein in patients with arteriosclerosis.

To sum up, this study found that FIB has a strong ability to predict VC. The results of this study have good clinical practical value, which is a necessary item for hospitalized patients, and the collection of

samples is simple. FIB can also be measured repeatedly, cheap, easily accepted by patients, and can be regulated by the use of drugs such as Bezafibrate. FIB is expected to become a new molecular marker for VC.

Abbreviations

VC=Vascular calcification; FIB=Fibrinogen; FDP=Fibrin degradation products; HDL=high-density lipoprotein; LDL=low-density lipoprotein

Declarations

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

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Tables

Table 1
Population analysis

Variables	Modeling Group	Verification Group	<i>P value</i>
Normal	202	71	
VC	139	50	
Age	60.842 ± 12.504	61.777 ± 11.840	0.474
High	168.748 ± 27.059	167.851 ± 10.772	0.723
Kg	71.891 ± 11.373	71.296 ± 12.751	0.635
Neutrophiles	0.637 ± 0.102	0.630 ± 0.105	0.562
Lymphocyte	0.269 ± 0.093	0.276 ± 0.096	0.447
FIB	3.272 ± 1.085	3.160 ± 0.898	0.313
FDP	3.571 ± 26.759	1.407 ± 3.854	0.376
Triglycerides	1.500 ± 1.145	1.586 ± 1.427	0.519
Cholesterol	4.495 ± 0.996	4.452 ± 1.053	0.694
HDL	1.050 ± 0.322	1.075 ± 0.253	0.457
LDL	2.801 ± 0.705	2.758 ± 0.738	0.584
Lipoproteins	286.245 ± 283.271	275.690 ± 293.930	0.736
Glutamyl transferase	29.080 ± 32.553	32.244 ± 29.112	0.350
CRP	12.962 ± 37.953	11.323 ± 36.595	0.694
FIB = Fibrinogen; FDP = Fibrin degradation products; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CRP = C-reactive protein			

Table 2
Univariate analysis of vascular calcification

Variables	Modeling Group	
	HR(95% CI)	P value
Neutrophiles	2074.501(99.313,43333.169)	< 0.00001
Lymphocyte	0.000(0.000,0.002)	< 0.00001
FIB	2.628(1.736, 3.978)	< 0.00001
FDP	1.498(1.123, 1.998)	0.00596
Triglycerides	0.974(0.755, 1.257)	0.83900
Cholesterol;	0.759(0.572, 1.007)	0.05574
HDL	0.036(0.009, 0.138)	< 0.00001
LDL	0.774(0.521, 1.150)	0.20525
Lipoproteins	1.003(1.002, 1.004)	< 0.00001
Glutamyl transferase	1.021(1.008, 1.034)	0.00117
CRP	1.134(1.070, 1.203)	0.00003
FIB = Fibrinogen; FDP = Fibrin degradation products; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CRP = C-reactive protein		

Table 3
Multivariate analysis of vascular calcification

Variables	Modeling Group	
	HR(95% CI)	P value
Neutrophiles	0.000 (0.000, 43.945)	0.17334
Lymphocyte	0.000 (0.000, 2.254)	0.06521
FIB	2.772 (1.307, 5.880)	0.00788
FDP	1.082 (0.702, 1.668)	0.72090
HDL	0.135 (0.023, 0.803)	0.02772
Lipoproteins	1.003 (1.001, 1.004)	0.00004
Glutamyl transferase	1.014 (0.997, 1.032)	0.09675
CRP	1.033 (0.970, 1.101)	0.30588
FIB = Fibrinogen; FDP = Fibrin degradation products; HDL = high-density lipoprotein; CRP = C-reactive protein		

Table 4
ROC curve analysis and optimal threshold analysis of the prediction model

Test	FIB	Lipoproteins	HDL
ROC area (AUC)	0.8018	0.7348	0.7019
95%CI low	0.7538	0.6785	0.6444
95%CI upp	0.8499	0.7912	0.7593
Best threshold	3.3050	182.2500	1.0850
Specificity	0.8543	0.6774	0.5376
Sensitivity	0.6403	0.7333	0.7926
Accuracy	0.7663	0.7009	0.6449
Positive-LR	4.3937	2.2733	1.7142
Negative-LR	0.4211	0.3937	0.3858
Diagnose-OR	10.4345	5.7750	4.4435
N-for-diagnose	2.0220	2.4346	3.0280
Postive-pv	0.7542	0.6226	0.5544
Negative-pv	0.7727	0.7778	0.7812
a	90	105	114
b	29	64	91
c	50	38	30
d	172	134	106

Figures

Figure 1

ROB curve of fibrinogen, lipoprotein and high-density lipoprotein on the vascular calcification prediction model