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Original Article

Diagnostic and predictive value of serum LDL/HDL and RBP4 levels in restenosis after revascularization in patients with coronary heart disease (CHD)

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Abstract: Percutaneous coronary intervention (PCI) is the principal treatment means for coronary artery stenosis lesions. However, it is prone to appear during postoperative restenosis. This study analyzed risk factors of coronary heart disease (CHD) restenosis after revascularization and discussed the diagnostic value of serum LDL/HDL ratio and RBP4. A total of 208 CHD patients with suspicious restenosis after PCI were collected, including 91 restenosis cases and 117 controls diagnosed by coronary angiography examination. Bilirubin, blood lipid, LDL/HDL ratio, RBP4, and Gensini score were compared. Their impacts on restenosis after CHD revascularization were analyzed by Logistic regression. The correlation among serum LDL/HDL ratio, RBP4, and Gensini score was analyzed by Spearman. The diagnostic value of serum LDL/HDL ratio and RBP4 was compared by ROC curve. Statistical difference was observed on gender, hypertension, diabetes, smoking, HDL, LDL/HDL, Gensini score, RBP4, and the diameter, length, and amount of stent between two groups ($P < 0.05$). Logistic regression analysis showed that diabetes, LDL/HDL, Gensini score, RBP4, and the diameter, length, and amount of stent were independent risk factors of restenosis. LDL/HDL and RBP4 were positively correlated with Gensini score. The area under the ROC curves of LDL/HDL and RBP4 were 0.808 and 0.786, respectively. Their sensitivities were 76.3% and 74.5%, while their specificities were 81.6% and 80.7%, respectively. LDL/HDL and RBP4 detections are of great significance in restenosis prediction after PCI. They are helpful to identify the high-risk restenosis patients after PCI, which is in favor of early intervention and prevention.

Keywords: Serum LDL/HDL, RBP4, coronary heart disease, restenosis after PCI, diagnosis

Introduction

Coronary atherosclerosis heart disease (CHD) is a type of vascular stenosis or obstruction induced by atherosclerosis. CHD has become the leading threat to human health with rising morbidity and mortality following the growth in the living standard, the change of dietary pattern, and the alteration of life style [1]. Interventional therapy is currently one of the main methods to CHD. In spite of the progress of medical technology, restenosis after interventional treatment is the key factor influencing the prognosis of patients [2]. The incidence of restenosis after stenting is between 10% and 20% [3]. Although DES reduces the restenosis rate lower than 10% [4], the pathophysiologic mechanism and prevention measures of restenosis is still a hotspot in the research of cardiovascular disease.

Atherosclerosis (AS) is a major risk factor for cardio-cerebrovascular disease and the fundamental pathological change of CHD. Abnormal lipid metabolism is the direct reason for AS formation. Numerous studies showed that blood lipid is an independent risk factor for cardiovascular disease [5]. However, the relationship of low density lipoprotein (LDL) and high-density lipoproteins cholesterol (HDL) with restenosis after PCI is still unclear, indicating that HDL and LDL may be associated with postoperative restenosis.

Retinol binding protein 4 (RBP4) is a kind of circulating adipose-derived factor from liver and

fat cells that widely distributes in blood, cerebrospinal fluid, urine, and other body fluids. RBP4 participates in AS, obesity, hypertension, and IR, suggesting that RBP4 may also involve in CHD [6]. Currently, various studies showed that serum RBP4 level obviously increased in CHD compared with normal control, while the role of RBP4 in restenosis after PCI is still unclear [6, 7]. Therefore, this study explored the relationship between RBP4 and restenosis after PCI.

Materials and methods

Subjects

A total of 208 CHD patients with suspicious restenosis after PCI were collected in The Affiliated Drum Tower Hospital of Nanjing, University Medical School, including 91 restenosis cases and 117 controls diagnosed by coronary angiography examination. Inclusion criteria: patients with CHD (as verified by CAG) and Gensini score (GS) > 40 were included, according to the diagnostic criteria of CHD (I25.105) based on the International Classification of Diseases 10th edition (ICD10). The exclusion criteria were: (1) myocardial bridge, cardiomyopathy, valvular heart disease, acute myocardial infarction; (2) clinical hyperthyroidism and hypothyroidism, hypothalamic or pituitary disease and other endocrine diseases; (3) complicated with cancer, acute cerebrovascular disease, severe infection, liver or kidney dysfunction, and hereditary hyperlipidemia; and (4) taking medications (such as an amine iodine ketones and other iodine-containing drugs, lithium agents, hormone preparations, interferon, phenytoin, dopamine and hormones). There were 136 males and 72 females with mean age at 59.34±10.46 (42-70) years old.

This study has been pre-approved by the Ethics Committee of The Affiliated Drum Tower Hospital of Nanjing, University Medical School. All subjects have signed the consent forms before recruitment in this study.

Testing index

Clinical information: Age, gender, hypertension history, and smoking history were recorded.

Serum index

The fasting blood was collected from all subjects to separate serum. Serum bilirubin, lipid, and RBP4 levels were detected. Bilirubin was observed as total bilirubin (TB) and direct bilirubin (DB). TB content was tested by vanadate method, while DB content was determined by diazonium method. Blood lipids are presented as cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL). TC and TG contents were detected by oxidase method, HDL content was assessed by direct enzymatic method, while LDL was calculated by Friedward formula. Serum RBP4 level was determined by ELISA.

Coronary arteriography

Selective left and right coronary angiography was performed using GE Innova3100 digital subtraction angiography system and Seldinger technique. Restenosis was diagnosed by artery luminal stenosis ≥ 50% within 5 mm range of the stent. Gensini integral method was used to assess stenosis degree. The weight coefficient was set according to different segment. 1-25% for 1 point, 26-50% for 2 points, 51-75% for 4 points, 76-90% for 8 points, 91-99% for 16 points, and 100% for 32 points. Gensini score was calculated according to the weight coefficient of lesion part and stenosis degree [8].

Statistical analysis

All data analyses were performed on SPSS 18.0 software. Measurement data are depicted as mean ± standard deviation and compared by t test. Enumeration data are presented as percentage or case number and compared by chi-square test. The impact of different index on restenosis was evaluated by Logistic regression analysis. The diagnostic value of serum LDL/HDL ratio and RBP4 was compared by ROC curve to calculate sensitivity and specificity. Significant test level was set at $\alpha = 0.05$.

Results

Clinical information analysis

No statistical difference was observed on age, TC, TG, LDL, TB, and DBI between two groups ($P > 0.05$). Gender, hypertension, diabetes, smoking, HDL, LDL/HDL, Gensini score, RBP4, and the diameter, length, and amount of stent showed obvious difference between two groups ($P < 0.05$) (**Table 1**).

Table 1. Clinical information comparison

Index	Control (n = 117)	Restenosis (n = 91)	t/χ^2	*P* value
Age	59.34±9.67	61.02±10.46	1.199	0.116
Gender/n (%)	69 (58.97)	67 (73.63)	4.855	0.028
Hypertension (%)	61 (52.14)	60 (65.93)	4.004	0.045
Diabetes (%)	28 (23.93)	35 (38.46)	5.118	0.024
Smoking/n (%)	58 (49.57)	59 (64.84)	4.845	0.027
BMI (kg/m^2)	23.74±2.81	24.68±3.04	2.309	0.011
TC (mmol/L)	4.16±0.71	4.23±0.92	0.600	0.275
TG (mmol/L)	1.53±0.96	1.68±0.92	1.138	0.128
HDL (mmol/L)	2.03±0.46	1.14±0.37	15.462	< 0.001
LDL (mmol/L)	2.08±0.87	2.25±0.69	1.572	0.059
LDL/HDL	1.03±0.26	1.92±0.24	25.32	< 0.001
TBI (μmol/L)	12.05±2.67	11.87±2.48	0.498	0.310
DBI (μmol/L)	4.56±1.35	4.45±0.97	0.683	0.248
Gensini score	17.89±7.58	30.91±10.57	9.931	< 0.001
RBP4 (mg/L)	45.62±7.94	60.58±9.05	12.677	< 0.001
Stent diameter (mm)	3.11±0.38	3.35±0.41	4.365	< 0.001
Stent length (mm)	25.08±6.07	26.56±5.58	1.807	0.036
Stent amount	1.35±0.51	1.56±0.62	2.615	0.005

Table 2. Multivariate Logistic regression analysis of restenosis after PCI

Index	Regression coefficient	Standard error	Wald value	*P* value	*OR* value	95% CI
Diabetes (%)	1.653	0.327	4.343	0.038	1.605	1.215~1.843
LDL/HDL	1.735	0.386	5.058	0.008	2.691	1.924~3.267
Gensini score	1.537	0.196	4.153	0.017	2.066	1.148~2.735
RBP4 (mg/L)	1.884	0.399	7.763	0.004	3.187	2.381~3.842
Stent diameter (mm)	1.679	0.308	5.905	0.014	2.121	1.263~2.584
Stent length (mm)	1.437	0.247	4.391	0.028	1.453	1.117~2.094
Stent amount	1.512	0.272	6.356	0.001	1.503	1.209~1.941

Table 3. Correlation analysis of serum LDL/HDL and RBP4 with Gensini score

Index	Gensini score	
	Spearman correlation coefficient *R*	*P*
LDL/HDL	0.482	0.001
RBP4	0.539	0.003

Multivariate logistic regression analysis of restenosis after PCI

Logistic regression analysis showed that diabetes, LDL/HDL, Gensini score, RBP4, and the diameter, length, and amount of stent were independent risk factors of restenosis (**Table 2**).

Correlation analysis of serum LDL/HDL and RBP4 with Gensini score

Spearman correlation analysis revealed that LDL/HDL and RBP4 were positively correlated with Gensini score (P < 0.05) (**Table 3**).

Diagnostic value analysis of LDL/HDL and RBP4 on restenosis after revascularization

LDL/HDL and RBP4 were selected to analyze their diagnostic value on restenosis after PCI. The area under the ROC curves of LDL/HDL and RBP4 were 0.808 and 0.786, respectively. Their sensitivities were 76.3% and 74.5% (**Figure 1**), while their specificities were 81.6% and 80.7%, respectively (**Table 4**).

Discussion

A variety of studies showed that coronary AS, diabetes, hypertension, male, smoking, hyperlipidemia, and the type, length, and number of stent are the risk factors of CHD recurrence [9, 10]. This study found that gender, hypertension, diabetes, smoking, HDL, LDL/HDL, Gensini score, RBP4, and the diameter, length, and amount of stent showed obvious difference between two groups. Logistic regression analysis showed that diabetes, LDL/HDL, Gensini score, RBP4, and the diameter, length, and amount of stent were independent risk factors of restenosis. Multiple research studies have demonstrated that the restenosis rate in male patients was significantly higher than that in female, while diabetes patient exhibited 1.92 times higher risk of restenosis compared with

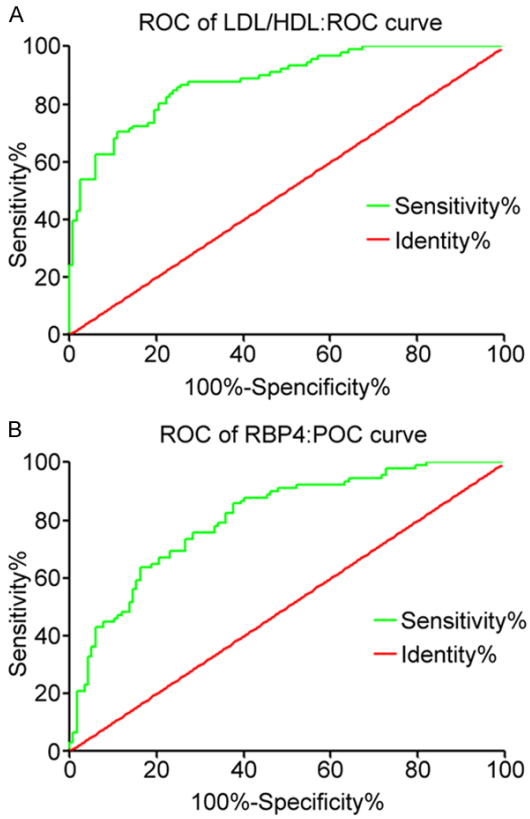

Figure 1. ROC curve analysis. A. ROC curve analysis of the diagnostic value of LDL/HDL on restenosis. B. ROC curve analysis of the diagnostic value of RBP4 on restenosis.

control [11, 12]. Kobayashi revealed that the restenosis rate was twice in stent length > 35 mm and average length at 13.5 mm compared with stent length ≤ 20 mm and average length at 9.5 mm [13]. Ellis found that the restenosis rate is as high as 64% in multiple overlapping stent site, which may be caused by larger metal density and multiple metal stents overlap leading to obvious endometrium hyperplasia. This study also found that LDL/HDL and RBP4 were two independent risk factors of restenosis except previous reports.

Lipid metabolism disorder is a traditional risk factor of AS. As one of the important elements of AS, while LDL can enter the blood vessel wall through vascular endothelial cells and be modified into oxidative LDL (OX-LDL). LDL elevation and OX-LDL formation are the key steps in inducing AS [14]. OX-LDL can induce endothelial cell apoptosis, change, and destroy the integrity of the endothelial cells, thus triggering cell adhesion molecule expression to facilitate mononuclear cells and endothelial cells adhesion and differentiate into macrophages within the blood vessels. The latter may phagocytize OX-LDL and lipids to form foam cell and accumulate cholesterol under endothelium [15-18]. Foam cells increase, fusion, and lipid composition eventually form the lipid core of AS plaque. Instead, HDL is treated as a lipoprotein with anti-AS function. HDL can transport cholesterol out of foam cells and to the liver for catabolism [19, 20]. In addition, HDL may play anti-AS role through anti-inflammation and antioxidant effect. For example, a high level of HDL inhibits LDL oxidative modification and restrains or reduces the pro-inflammatory role of OX-LDL. HDL-C over 1.55 mmol/L is considered as a protective factor for CHD. However, there is still lack of reports about the relationship between HDL and LDL with restenosis after stenting. Clinical research demonstrated that lipid-lowering drug is effective to prevent restenosis, revealing the close relationship between HDL and LDL with restenosis after stenting [3]. This study confirmed that LDL/HDL was an independent risk factor of restenosis after PCI by Logistic regression analysis. Spearman correlation analysis revealed that LDL/HDL was positively correlated with Gensini score. Further analysis exhibited that LDL/HDL was associated with the stenosis degree of coronary artery. ROC curve analysis demonstrated that the area under the ROC curve of LDL/HDL was 0.808, while the sensitivity and specificity was 76.3% and 81.6%, respectively, indicating that LDL/HDL exhibited high sensitivity and specificity in restenosis diagnosis and prediction.

Table 4. Diagnostic value analysis of LDL/HDL and RBP4 on restenosis after revascularization

Index	AUC	Youden index	Sensitivity	Specificity
LDL/HDL	0.808	0.579	76.3%	81.6%
RBP4	0.786	0.552	74.5%	80.7%

RBP4 participates in obesity, metabolic disease, and insulin resistance by inhibiting phosphatidyl-inositol-3 kinase (PIK) activity and other pathways [21-23]. Therefore, scholars speculated that RBP4 may be associated with CHD. Current studies reported that serum RBP4 level was obviously higher in CHD patients compared with normal control, while it was mar-

kedly higher in CHD patients combined T2DM or high disease degree [6, 24]. Correlation analysis showed that serum RBP4 level was positive correlated with waistline, WHR, BMI, SBP, TC, TG, FINS, FPG, LDL-C, and HOMA-IR in CHD patients. Multivariate regression analysis revealed that RBP4 was related to TG and HDL-C, indicating its association with high-risk factors of CHD, such as central obesity, lipid metabolism, and IR. This study found that serum RBP4 level was significantly higher in restenosis patients compared with control. Further Logistic regression analysis confirmed that RBP4 was an independent risk factor of restenosis (OR = 3.187, 95% CI = 2.381-3.842). Park SE demonstrated that serum RBP4 was related to hs-CRP level, while RBP4 mRNA was positively correlated with MCP-1 and CD68, suggesting that RBP4 participates in inflammation in CHD [25]. Moreover, serum RBP4 was found to be negatively correlated with adiponectin that can protect AS, revealing that RBP4 can promote the occurrence and development of cardiovascular disease. ROC curve analysis demonstrated that the area under the ROC curve of RBP4 was 0.786, while the sensitivity and specificity was 74.5% and 80.7%, respectively, suggesting that RBP4 showed high sensitivity and specificity in restenosis diagnosis and prediction. Further analysis could be taken to evaluate the ROC curve of combined detection.

Conclusion

LDL/HDL and RBP4 detection are of great significance for the diagnosis and prediction of restenosis after PCI. They are helpful to identify the high-risk restenosis patients after PCI, which is in favor of early intervention and prevention.

Disclosure of conflict of interest

None.

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