

## Original Article

# The correlation of visfatin, MMP-9 and insulin resistance in patients with coronary heart disease

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**Abstract:** Background: This study was aimed to determine the association between serum levels of visfatin and matrix metalloproteinase 9 (MMP-9) and homeostasis model assessment-insulin resistance (HOMA-IR) in patients with coronary heart disease (CHD). Materials and methods: During November 2009 and March 2011, CHD patients and non-CHD patients (controls) receiving coronary arteriography were selected. Eligible CHD patients were classified into two groups of CHD with insulin resistance (IR) and CHD without IR. The serum biochemical indexes including the levels of visfatin and MMP-9 in CHD patients and the cut-off values of them for CHD with IR were measured. Results: Total 32 CHD patients with IR (12 male, 20 female), 28 CHD patients without IR (11 male, 17 female) and 20 control patients (12 male, 35 female) were enrolled. The serum concentration of visfatin and MMP-9 among control group, CHD without IR group and CHD with IR group were significantly different ( $P < 0.05$  for all). In patients with CHD, the HOMA-IR and Gensini's score were both positively correlated with serum levels of visfatin ( $r = 0.5549$ ,  $P < 0.01$ ;  $r = 0.6231$ ,  $P < 0.01$ ) and MMP-9 ( $r = 0.4211$ ,  $P < 0.01$ ;  $r = 0.6179$ ,  $P < 0.01$ ). Furthermore, there was a positive correlation between visfatin and MMP-9 ( $r = 0.6377$ ,  $P < 0.01$ ), as well as between Gensini's score and HOMA-IR ( $r = 0.5023$ ,  $P < 0.01$ ). The cut-off values of visfatin and MMP-9 were 40.25 ng/ml and 443.21 ng/ml, respectively. Conclusions: HOMA-IR may be a risk factor for CHD. Serum concentrations of visfatin and MMP-9 could be positive correlated with CHD and HOMA-IR.

**Keywords:** Insulin resistance, coronary heart disease, visfatin, matrix metalloproteinase-9

## Introduction

Coronary heart disease (CHD) is a group of diseases including stable angina, unstable angina, myocardial infarction, and sudden coronary death [1]. CHD is one of the most common cause of death in 2013 globally, resulting in 8.14 million deaths up from 5.74 million deaths in 1990 [2]. In the developed countries like the USA, CHD is the leading cause of death, yet risk assessment for its development remains challenging [3].

Homeostasis model assessment-insulin resistance (HOMA-IR) can lead to clinical cardiovascular complications, especially in patients with CHD [4, 5]. A previous study indicates that HOMA-IR is a powerful predictor for CHD, and HOMA-IR accentuates the risk of CHD [6]. Visfatin has been found to be highly expressed in adipose tissue [7]. The increased level of visfatin can down-regulate the insulin receptors and

eventually aggravate HOMA-IR, which shows that visfatin may play an important role in preventing the occurrence of IR [8]. Visfatin is an adipocytokine with proinflammatory property, it induces the secretion of inflammatory cytokines such as IL-8, TNF- $\alpha$  and IL-6 [9]. Besides, visfatin in patients with acute coronary syndrome (ACS) is highly expressed [10]. These evidences show that visfatin may be associated with the occurrence of CHD [11]. Matrix metalloproteinase 9 (MMP-9) is a member of the fulleren family and is significantly increased in patients with type II diabetes, which potentially contribute to the risk of cardiovascular disease [12, 13]. MMP-9 plays an important role in the degradation of extracellular matrix (ECM) and basement membrane [14]. It is highly expressed in patients with ACS and in patients in-stent restenosis, thus it may be used as a risk factor for CHD [15, 16]. Although previous researches on visfatin and MMP-9 have focused on the

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mechanism of atherosclerosis, the correlation among visfatin, MMP-9 and HOMA-IR in patients with CHD is still unclear.

In the present pilot study, a case control research was performed to investigate the correlations among visfatin, MMP-9 and HOMA-IR in patients with CHD. We hoped to further verify the important role of HOMA-IR in CHD and reveal whether visfatin and MMP-9 could be used as early predictors for CHD in clinical intervention.

### Materials and methods

#### *Patients and exclusion criteria*

Patients with and without CHD undergoing coronary arteriography in the inpatient and outpatient service in the first hospital of Jilin university from November 2009 to March 2011 were enrolled in the study. The CHD patients were excluded if they: i) had undergone coronary intervention; ii) had serious infectious diseases, such as infection in the respiratory tract, biliary, or tissue etc; iii) with malignant tumors; iv) with acute hepatic and kidney dysfunction; v) with rheumatic disease and connective tissue disease, and vi) had incomplete medical records. The standard of WHO according to the clinical features and electrocardiographic changes were used for the diagnose of CHD [17]. The selective coronary arteriography of CHD patients showed  $\geq 50\%$  diameter stenosis in at least one coronary vessel. The study was approved by the institutional ethics committee, and all patients gave written informed consent.

#### *Group division*

HOMA [18] was taken to evaluate HOMA-IR of participants:  $\text{HOMA-IR} = \text{fasting plasma glucose (FPG, mmol/L)} \times \text{fasting insulin (FINS, } \mu\text{U/L)} / 22.5$ .  $\text{HOMA-IR} \geq 2.8$  was defined as IR. Then CHD patients were divided into two subgroups: CHD with IR ( $\text{HOMA-IR} \geq 2.8$ ) and CHD without IR ( $\text{HOMA-IR} < 2.8$ ). The non-CHD patients were classified into the control group.

#### *Gensini's score of CHD*

Gensini's score system [19] in patients with CHD was adopted to stratify patients into three groups by the severity of coronary atherosclerosis:

mild atherosclerosis (Gensini score, 1-25), moderate atherosclerosis (Gensini score, 25-49) and severe atherosclerosis (Gensini score,  $\geq 50$ ). According to the scoring system, the severity of CHD with coronary artery stenosis  $\leq 25\%$ , 26%-50%, 51%-75%, 76%-90%, 91%-99% and 100% were scored as 1, 2, 4, 8, 16 and 32 point, respectively. Each point was multiplied with separate coefficients based on the coronary artery segments: these coefficients were 5 for left coronary, 2.5 for anterior interventricular branch, 1.5 for the middle, 0.5 for the second diagonal branch, 2.5 for the left circumflex branch, and 1 for the others including distal and posterior descending branch. The points were added and the total Gensini points were calculated for each CHD patients.

#### *Basic clinical and laboratory characteristics*

The detailed records of every subject about sex, age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and smoking history were reviewed. Meanwhile, impaired fasting glucose (IFG), FINS, triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), as well as other biochemical indicators were detected.

#### *Detection of serum visfatin and MMP-9*

The serum levels of visfatin and MMP-9 for all participants were measured by the Enzyme Linked Immuno Sorbent Assay (ELISA) kit (R&D Systems, Minneapolis, Minnesota, USA). This assay was performed according to the conventional ELISA technique and the manufacturer's instruction manual [20].

#### *Statistical analysis*

The cut-off values of serum visfatin and MMP-9 for the diagnosis of CHD with IR were obtained using receiver operating characteristic (ROC) curve. At each percentage score, the sensitivity and specificity for each outcome under study was plotted. The area under the ROC curve represented the probability of distinguishing between CHD with IR and CHD without IR individuals correctly. On the basis of this model, the prediction value was calculated followed by ROC curve analysis. The score having the closest distance to the point with both maximum sensitivity and specificity was selected as the

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**Table 1.** The general information and clinical data of patients in three groups

Characteristics	Groups			Chi-Square/F	P
	Control	CHD without IR	CHD with IR		
Cases	20	28	32		
Smoking cases	9	15	20	1.558	0.459
Sex (male/female)	12/8	11/17	12/20	2.881	0.237
Age	51.45 ± 6.63	55.89 ± 6.91 <sup>a</sup>	57.13 ± 6.12 <sup>a</sup>	4.843	0.01
BIM (kg/m <sup>2</sup> )	22.41 ± 2.27	22.89 ± 1.65	25.06 ± 1.67 <sup>a,b</sup>	16.503	< 0.001
Systolic blood pressure (mmHg)	117.50 ± 8.80	120.07 ± 8.32	127.31 ± 7.21 <sup>a,b</sup>	10.910	< 0.001
Diastolic blood pressure (mmHg)	76.05 ± 4.13	79.14 ± 7.04	82.09 ± 6.11 <sup>a</sup>	6.229	0.003
Fasting glucose (mmol/L)	4.36 ± 0.43	5.05 ± 0.41 <sup>a</sup>	5.34 ± 0.38 <sup>a,b</sup>	36.747	< 0.001
Total cholesterol (mmol/L)	4.18 ± 0.58	4.55 ± 0.54 <sup>a</sup>	5.02 ± 0.62 <sup>a,b</sup>	13.348	< 0.001
HDL-C (mmol/L)	1.36 ± 0.11	1.24 ± 0.14 <sup>a</sup>	1.11 ± 0.16 <sup>a,b</sup>	19.59	< 0.001
LDL-C (mmol/L)	1.93 ± 0.48	2.22 ± 0.49 <sup>a</sup>	2.57 ± 0.45 <sup>a,b</sup>	11.766	< 0.001
Triglycerides (mmol/L)	1.33 ± 0.32	1.57 ± 0.39 <sup>a</sup>	1.81 ± 0.47 <sup>a,b</sup>	8.63	< 0.001
FINS (uIU/ml)	9.49 ± 3.48	10.41 ± 3.25	14.37 ± 4.34 <sup>a,b</sup>	13.032	< 0.001
HOMA-IR	2.02 ± 0.48	2.26 ± 0.37	4.05 ± 0.72 <sup>a,b</sup>	110.435	< 0.001

CHD: Coronary heart disease; BMI: Body mass index; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; FINS: Fasting insulin; HOMA-IR: Homeostasis model assessment-insulin resistance; <sup>a</sup>P < 0.05 compared with the control group; <sup>b</sup>P < 0.05 compared with the CHD without IR group.

cut-off score leading to the greatest number of CHD which were correctly classified as having IR.

All data were expressed as the mean ± standard deviation (SD). Statistical analysis was performed by the SPSS13.0 software (SPSS Inc., Chicago, IL, USA). Normality of distribution was assessed with Kolmogorov-Smirnov test. The qualitative data was analyzed by chi square test, while the quantitative variables were analyzed by one way ANOVA test followed by Fisher's least significant difference (LSD) pair wise comparisons. The severity of CHD between CHD with IR group and CHD without IR group was revealed by Mann-Whitney Test. Correlations between changes in Gensini's score, HOMA-IR, the serum levels of visfatin (ng/ml) and MMP-9 (ng/ml) were analyzed by Pearson correlation analysis. *P* < 0.05 was considered to be significant difference.

### Results

#### *The general clinical data*

Total 60 CHD patients (age range: 40~68; mean age: 55.42 ± 6.60; 23 male, 37 female), including 32 in the CHD with IR group (mean age: 57.13 ± 6.12; 12 male, 20 female) and 28 in the CHD without IR group (mean age: 55.89

± 6.91; 11 male, 17 female), as well as 20 control patients (age range: 40~62; mean age: 51.45 ± 6.63; 12 male, 35 female) were involved in our study.

There were no significant differences of smoking and sex among three groups (*P* > 0.05). Age, BMI, SBP, DBP, FPG, TG, TC, LDL-C and FIN in the CHD with IR group were higher than those of the control group (all *P* < 0.05), but HDL-C concentration in the CHD with IR group was lower than that of the control group (*P* < 0.05). BMI, FPG, TG, TC, LDL-C, FINS in the CHD with IR group were higher than those in the CHD without IR group (all *P* < 0.05), but HDL-C level in the CHD with IR group was lower than that in the CHD without IR group (*P* < 0.05). However, there was no significant difference of DBP between the CHD with IR group and the CHD without IR group (*P* > 0.05). The levels of FPG, TG, TC, LDL-C in the CHD without IR group were higher than those in the control group, but HDL-C in CHD without IR group was lower than that in the control group (*P* < 0.05). The HOMA-IR of the CHD with IR group was significantly higher than that in the CHD without IR group and the control group (all *P* < 0.05). Furthermore, the HOMA-IR of the CHD without IR group was significantly higher than that in the control group (*P* < 0.05). The detail information was listed in **Table 1**.

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**Table 2.** The variability in the severity of coronary artery stenosis between CHD with IR group and CHD without IR group

Group	Severity of coronary artery stenosis			P score
	Mild atherosclerosis group	Moderate atherosclerosis group	Severe atherosclerosis group	
CHD with IR	7 (21.9%)	10 (31.2%)	15 (46.9%)	0.005
CHD without IR	15 (53.6%)	8 (28.6%)	5 (17.8%)	

CHD: Coronary heart disease; IR: Insulin resistance.

**Table 3.** The variability of visfatin and MMP-9 among groups

	Control group (n = 20)	CHD without IR (n = 28)	CHD with IR (n = 32)	F	P
Serum concentration of visfatin (ng/ml)	22.24 ± 7.79	38.34 ± 14.07 <sup>a</sup>	51.47 ± 16.41 <sup>a,b</sup>	27.438	< 0.001
Serum concentration of MMP-9 (ng/ml)	227.18 ± 100.60	412.97 ± 161.94 <sup>a</sup>	649.63 ± 213.17 <sup>a,b</sup>	38.293	< 0.001

CHD: Coronary heart disease; MMP-9: Matrix metalloproteinase 9. <sup>a</sup>P < 0.05 compared with the control group; <sup>b</sup>P < 0.05 compared with the CHD without IR group.

### *The variation of the severity of coronary artery stenosis between CHD with IR group and CHD without IR group*

In the CHD with IR group, a total of 7 patients had mild atherosclerosis (21.9%), 10 patients had moderate atherosclerosis (31.2%) and 15 patients had severe atherosclerosis (46.9%). In CHD without IR group, there were 15 patients had mild atherosclerosis (53.6%), 8 patients had moderate atherosclerosis (28.6%) and 5 patients had severe atherosclerosis (17.8%). There was significant difference of percent composition of coronary artery stenosis severity between the CHD with IR group and the CHD without IR group (P = 0.005). The detail information was listed in **Table 2**.

### *The variability of visfatin and MMP-9 among groups*

The results showed that the serum levels of visfatin and MMP-9 were gradually increased from the control group, to the CHD without IR group, then to the CHD with IR group (**Table 3**). Moreover, the differences among three groups were significant (all P < 0.05).

### *The analysis of correlation between indexes in patients with CHD*

Pearson correlation analyses showed that the correlations between HOMA-IR and Gensini's score (r = 0.5023, P < 0.01), serum concentration of visfatin and HOMA-IR (r = 0.5549, P < 0.01), serum MMP-9 concentration and HOMA-

IR (r = 0.4211, P < 0.01), serum visfatin concentration and serum MMP-9 concentration (r = 0.6377, P < 0.01), serum visfatin concentration and Gensini's score (r = 0.6231, P < 0.01), serum MMP-9 concentration and Gensini's score (r = 0.6179, P < 0.01), were all highly significant (**Figure 1**).

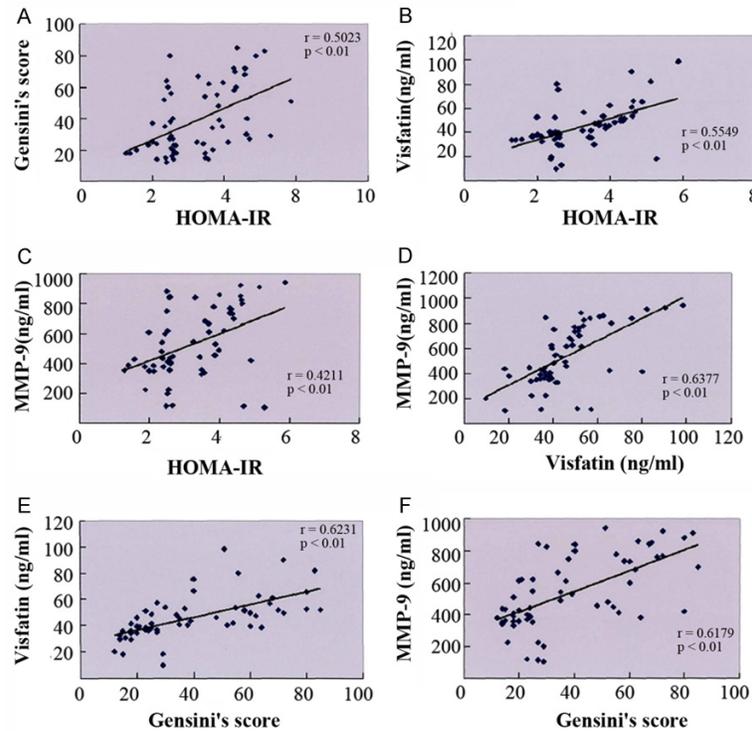
### *The cut-off scores of visfatin and MMP-9*

The cut-off values for optimal diagnostic efficiency determined by ROC curve analysis were 40.25 ng/ml for visfatin, and 443.21 ng/ml for MMP-9. The areas under the ROC curves for visfatin and MMP-9 were 0.834 [95% CI, 0.721-0.946, < 0.05] and 0.731 [95% CI, 0.598-0.864, P < 0.05], respectively. According to the cut-off values, the sensitivities of visfatin and MMP-9 for the diagnosis of CHD with IR were 87.5% and 78.1%, respectively, and the specificities of them were 85.7% and 67.9% (data not shown).

## **Discussion**

CHD is one of the most common form of ischemic cardiovascular disease at present [21]. Both CHD and diabetes associated with HOMA-IR are major causes of morbidity and mutually influenced each other [22, 23]. A previous study indicates that HOMA-IR is a contributing factor for coronary artery stenosis, while increased levels of visfatin and MMP-9 are found to contribute to the development and complication of atherosclerosis [24]. In the present study, the plasma concentrations of visfatin and MMP-9,

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**Figure 1.** The results of correlation analysis between index changes in patients with coronary heart disease (CHD). A: The correlation between homeostasis model assessment insulin resistance (HOMA-IR) and Gensini's score ( $r = 0.5023$ ,  $P < 0.01$ ); B: The correlation between HOMA-IR and the concentration of visfatin in CHD group ( $r = 0.5549$ ,  $P < 0.01$ ); C: The correlation between HOMA-IR and the concentration of MMP-9 in CHD group ( $r = 0.4211$ ,  $P < 0.01$ ); D: The correlation between the concentration of visfatin and MMP-9 in CHD group ( $r = 0.6377$ ,  $P < 0.01$ ); E: The correlation between Gensini's score and the concentration of visfatin ( $r = 0.6231$ ,  $P < 0.01$ ); F: The correlation between Gensini's score and the concentration of Matrix metalloproteinase-9 (MMP-9) ( $r = 0.6179$ ,  $P < 0.01$ ).  $r$  = Pearson correlation coefficient.

and the clinical data among CHD patients with IR or not, as well as that of control participants were different. The results revealed that proteins including visfatin and MMP-9 may be used as the early predictors of CHD.

Pearson correlation analysis was used to analyze the relationship between Gensini's score and HOMA-IR, and the result showed that they were positively correlated ( $r = 0.5023$ ,  $P < 0.01$ ). Hanley *et al.* [25] indicated that the likelihood of occurrence of cardiovascular disease can be increased by more than 2 times following the increased HOMA-IR index. Baldasseroni *et al.* suggested that HOMA-IR can be an independent predictor of atherosclerosis by affecting epicardial adipose tissue [26]. Thus, we concluded that HOMA-IR may be associated with the severity of coronary stenosis, and may be one of the risk factors for CHD. In addition,

in this study, a positive correlation between the serum level of visfatin and Gensini score ( $r = 0.6231$ ,  $P < 0.01$ ) was found, which showed that serum visfatin may be associated with the severity of coronary stenosis. A previous study indicated that visfatin has various biological activities [27]. It could induce phosphorylation of insulin receptor on tyrosine residues and active the MAPK signal pathway, which is similar with the way of insulin [28]. Chen *et al.* indicated that visfatin can down regulate the expression of insulin receptors and aggravate HOMA-IR, which means it plays an important role in preventing IR [29]. Furthermore, visfatin which affects not only the metabolism of glucose and lipid, but also the function of endothelial cell and promotes angiogenesis, participates in the process of inflammation and plays an important role in ankylosing spondylitis [11, 30]. The increased extent of coronary stenosis could result in the improved serum visfatin concentration [31]. In the

present study, the serum concentration of visfatin gradually increased in CHD groups, which suggested that the visfatin concentration was associated with the progress of CHD. Furthermore, this study showed a positive correlation between the visfatin concentration and the corresponding HOMA-IR ( $r = 0.5549$ ,  $P < 0.01$ ) in CHD patients, which also proved this point.

MMP-9 is important for vascular basement membrane mainly via the over-degrading type IV collagen [32, 33]. It can lead to invasion and migration of vascular smooth muscle cells in to the intima, and secretion of ECM, followed by promote the formation of plaque [34]. A previous research also showed that the MMP-9 level in patients with type II diabetes was significantly increased, while HOMA-IR and serum MMP-9 level was reduced after the treatment of IR, such as by changes in lifestyle [35] and

the use of PPAR $\gamma$  activator [36, 37]. In the present study, there was a positive correlation between the serum level of MMP-9 and Gensini score ( $r = 0.6179$ ,  $P < 0.01$ ), which indicated that the serum MMP-9 level is related with the extent of coronary stenosis. Therefore, MMP-9 maybe a risk factor potentially associated with the development and progression of insulin-related cardiovascular diseases. Furthermore, previous studies indicated that visfatin is involved in the regulation of some inflammatory factors, including upregulating MMP-9, activating MMP-9 in monocytes, and increasing production of MMP-2/-9 and monocyte chemoattractant protein-1 (MCP-1) in endothelial cells [38, 39]. However, whether visfatin could regulate the expression and the activity of MMP-9 is rarely reported. In this study, the positive correlation between the serum levels of visfatin and MMP-9 ( $r = 0.6337$ ,  $P < 0.01$ ) was revealed. In addition, visfatin was found to enhance the degradation of matrix mediated by MMP-9, and can promote the expression of multiple genes [40]. In the present preliminary study, the relationship between visfatin and MMP-9 was discussed. Moreover, we try to distinguish CHD with/out IR by these two parameters, and the cut-off scores with optimal diagnostic accuracy for CHD with IR were obtained. This combined detection of the two factors may help to detect CHD in clinical practice. While a large number of clinical and animal experiments were needed to confirm the results.

In conclusion, the present study indicated that HOMA-IR would be a risk factor for CHD. Serum visfatin and MMP-9 were positively related with CHD and IR. Furthermore, the serum concentrations of visfatin and MMP-9 combined with coronary angiography may benefit for the detection, monitoring and management of coronary stenosis in patients with CHD. However, some limitations to this pilot study should be mentioned, such as the small sample size and the absence of follow-up study. Further investigations aimed at assessing the predictive value of visfatin and MMP-9 levels on insulin-related CHD in clinical practice are needed.

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### Disclosure of conflict of interest

None.

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