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Plasma levels of omentin−1 and visfatin in senile patients with coronary heart disease and heart failure

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ABSTRACT

Objective: To investigate the alteration of plasma levels of omentin−1 and visfatin in elderly patients with coronary heart disease (CHD) and heart failure. **Methods:** Plasma omentin−1 and visfatin levels were measured in 90 subjects (29 stable angina pectoris (SAP) cases, 30 unstable angina pectoris (UAP) cases and 31 age− and sex−matched healthy controls (age $\geqslant$ 60 years) by enzyme−linked immunosorbent assay methods. According to the New York Heart Association classification, 59 CHDs were divided into three groups: functional I class, 11 cases; functional II /III class, 36 cases; and functional IV class, 12 cases. **Results:** The plasma level of omentin−1 in CHD patients was significantly lower than that of the control group. Omentin−1in SAP group and UAP group were significantly lower compared to the control group (there was no statistical significance between UAP group and SAP group; $P>0.05$). The plasma level of visfatin in CHD patients was significantly higher than that of the control group. Similarly, visfatin in SAP group and UAP group were all significantly higher compared to the control group, while there was no statistical significance between UAP group, and SAP group. The plasma omentin−1 level was negatively correlated with SBP ($r=-0.264$, $P<0.05$), positively correlated with HDL−c level ($r=0.271$, $P<0.05$); the plasma visfatin level was positively correlated with TC ($r=0.292$, $P<0.05$), negatively correlated with HDL−c level ($r=-0.266$, $P<0.05$). There was a negative correlation between plasma omentin−1 and visfatin levels ($r=-0.280$, $P<0.05$). Moreover, multiple linear stepwise regression analysis showed that omentin−1 and visfatin levels might be affected by HDL−c level. Logistic regression analysis showed that visfatin could be an independent risk factor of CHD. **Conclusions:** Decreased levels of omentin−1 and increased levels of visfatin may be involved in the occurrence and development of CHD. Omentin−1 and visfatin, independently, may be protective and pro−inflammatory cytokines. Additionally, both omentin−1 and visfatin may be related to lipid metabolism. Visfatin may be an independent risk factor of CHD.

1. Introduction

Coronary heart disease (CHD) is one of the primary diseases leading to death worldwide. CHD is due to coronary atherosclerosis (AS) stenosis or occlusion that leads to

myocardial ischemia hypoxia. Coronary artery disease (CAD) not only includes lipid accumulation within the artery wall; it also involves inflammatory reactions and other immune processes in the occurrence and development of AS. Recent studies have found that in addition to regulating glucose and lipid metabolism, some adipocytokines, such as omentin and visfatin, also play an important role in regulating immune response and inflammation[1].

In 2003, Yang et al[2] suggested omentin as a new adipocytokine secreted from the omental adipose tissue. Omentin was demonstrated to enhance insulin−mediated

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glucose–uptake in adipocytes, activate proteinkinase Akt/PKB, and improve the insulin sensitivity of fat cells. Yamawaki et al[3] demonstrated for the first time that omentin plays an anti–inflammatory role by preventing the TNF– α –induced COX–2 expression in vascular endothelial cells. Kazama et al[4] found that omentin inhibits TNF– α –induced inflammation of invascular smooth muscle cells (SMCs), and its anti–inflammatory role is attributed, at least in part, to the inhibition of superoxide production. Omentin has two isoforms: omentin–1 and omentin–2; omentin–1 was shown to be the major circulating isoform in human plasma[3]. In addition, omentin–1 was also regarded as a protective cytokine in the metabolic imbalance condition of the body[5]. Previous research found that the plasma levels of omentin were decreased in patients with CHD, which indicated that omentin–1 may also be involved in the occurrence of coronary AS. However, research in the involvement of omentin in the development of heart failure patients with CHD is limited.

In 2005, Fukuhara et al[6] discovered visfatin–another adipocytokine mainly secreted from visceral adipose tissue that has+ insulin–mimetic effects and roles in glucose and lipid metabolism regulation. The inflammatory response, immune regulation, and other biological activity are closely associated with obesity, type 2 diabetes and insulin resistance. Sonoli et al[7] found that visfatin had antiapoptotic activity and had a regulatory role in inflammation. Plasma levels of visfatin increased with the increase of C–reactive protein (CRP) levels, further suggesting visfatin's inflammatory effects[8]. Relevant research indicated that these inflammatory effects increased the risk of cardiovascular events in patients with obesity. Malyszko et al[9] reported that visfatin is also related to hs–CRP. Moreover, several studies have found that visfatin can up–regulate the expression of inflammatory cytokines (such as IL–6, IL–8, MCP–1), and consequently, these inflammatory cytokines can increase the expression of visfatin, thus accelerating the development of cardiovascular disease. Taken together, these research results suggest that there may be a close link between inflammation and adipokines. Other studies, however, found that visfatin had no correlation with hs–CRP; thus, visfatin may be unrelated to the pro–inflammatory effect. Although there are arguments about whether visfatin is a pro–inflammatory cytokine or an anti–inflammatory factor, recent studies lean towards the claim that visfatin is a novel inflammatory regulator with pro–inflammatory effects. Lastly, research suggests that visfatin also plays an important role in the process of unstable atherosclerotic plaque[10]; however, the mechanism of visfatin in cardiovascular diseases is still not clear. Therefore, our study's aim is to observe the changes of plasma omentin–1 and visfatin levels, and discuss their effects in the occurrence of CHD within a group of elderly CHD patients.

2. Materials and methods

2.1. Research objects

All patients were selected at the Second Xiangya Hospital of Central South University from July 2012 to December 2012 by coronary angiography or coronary CT angiography. Fifty–nine elderly patients diagnosed with CHD were chosen and 31 healthy subjects served as a control group. All subjects were aged over 60 years. Based on clinical symptoms, the CHD group was divided into two groups: a stable angina pectoris (SAP) group and an unstable angina pectoris (UAP) group. With regards to the CHD grading of New York Heart Association (NYHA) classification method, the CHD group was divided into three groups based on the conscious activity found within patients, namely functional Ⅰ class, 11 cases; functional Ⅱ/Ⅲ, class 36 cases; and functional Ⅳ, class 12 cases. All subjects signed informed consent.

2.2. Diagnostic criteria

Stable angina pectoris is due to typical angina pectoris attack caused by myocardial ischemia and hypoxia. Its clinical manifestation is relatively stable within 1 to 3 months, with same pain–onset time daily and weekly, with equal emotional and labor pain evoked, and with no changes in nature/ range/ duration in each attack. Relief time of pain is also similar with nitroglycerin.

Unstable angina pectoris is a formerly stable angina pectoris. Within one month, the pain increased seizure frequency, severity, and duration. Factors, such as nitrates, with alleviating effect are reduced. Moreover, new angina pectoris occur within one month and pain occurs due to lighter load; it can occur while at rest or can be induced by slight activity.

Heart function classification: according to the NYHA classification method proposed in 1928, the degree of activity induced heart failure symptoms and heart function was divided into four levels.

Diagnostic criteria of the elderly: in accordance with the elderly branch of standard Chinese Medical Association in 1990, subjects should be 60 years of age or older.

2.3. Exclusion criteria

Subjects with the following were excluded: severe liver/ kidney dysfunction; severe systemic disease (such as the diseases of respiratory system/ digestive system/ nervous system etc.); malignant tumor; acute/ chronic infectious

diseases; autoimmune disease or connective tissue disease; and a major trauma or surgical operation over the past three months.

2.4. Apparatus and reagents

The following apparatus were used: 80-2 desktop centrifuge, produced by the Shanghai Operation Machinery Factory; ELX800 automatic enzyme-mark analyzer, manufactured by Bio-EK Instrument Inc; Omentin ELISA kit and visfatin ELISA kit, provided by Wellbiotechnology Company, Changsha.

2.5. Research methods

2.5.1. Sample processing
All subjects admitted to the hospital fasted for 10 h. Height, weight, and blood pressure were measured. Subsequently, venous blood was drawn the following morning for routine blood test, liver and kidney function test, C reactive protein test and so on (Department of laboratory quality control index by special inspection). At the same time, 3 mL elbow venous blood was transferred into EDTA anticoagulant tubes, shaken, and centrifuged at 2 000 r/min 20 min. The supernatant was then stored at -80 ℃, to be used for the determination of plasma concentration of omentin -1 and visfatin.

2.5.2. Determination of plasma Omentin-1
Plasma concentrations of omentin-1 were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Wellbiotechnology Company, Chang sha) with detection range of 50 ng/L to 1 000 ng/L.

2.5.3. Determination of plasma visfatin
Plasma concentrations of visfatin were determined using an ELISA kit (Wellbiotechnology Company, Changsha) wih detection range of 1 μ g/L to 20 μ g/L.

2.6. Statistical analysis

The data were analyzed using the statistical package SPSS 17.0. Measurement data were expressed as mean$\pm$ SEM. Normality and homogeneity of variance test were used for each group. Differences were evaluated by two-tailed Student's t test or ANOVA. Pearson analysis method was used for correlation analysis. Multiple factors were analyzed by multiple linear stepwise regression analysis. Logistic regression analysis was applied to evaluate the correlation between the independent variables and CHD. Statistical significance was set at $P<0.05$.

3. Results

3.1. General information

The clinical and biochemical characteristics of the study subjects are provided in Table 1. Compared with the control group, the CHD group'sBody Mass Index (BMI) and serum levels of TC, TG, and CRP increased significantly, while serum levels of HDL-c decreased significantly. There was a significant statistical difference between the two groups ($P<0.05$), but there were no significant changes in age, blood pressure, LDL-c, ALT, AST, BUN, and Cr between the two groups ($P>0.05$).

Table 1

Characteristics of study subjects in CHD and Control group.

Indexes	Control group (n=31)	CHD group (n=59)	P value
Sex(male/femele)	20/11	36/23	
Age (years)	75.85$\pm$8.99	73.90$\pm$8.39	0.321
BMI (Kg/m2)	22.32$\pm$2.61	24.05$\pm$2.92	0.007
SBP (mmHg)	132.84$\pm$12.55	134.83$\pm$14.31	0.515
DBP (mmHg)	75.81$\pm$7.92	74.81$\pm$10.31	0.641
TC (mmol/L)	4.20$\pm$0.57	4.72$\pm$0.86	0.004
TG (mmol/L)	1.20$\pm$0.48	1.55$\pm$0.62	0.006
LDL-C (mmol/L)	2.72$\pm$0.78	2.85$\pm$1.03	0.542
HDL-C (mmol/L)	1.20$\pm$0.22	1.03$\pm$0.23	0.001
ALT (μ/L)	15.82$\pm$6.19	20.74$\pm$14.96	0.080
AST (μ/L)	20.92$\pm$4.94	22.76$\pm$8.81	0.283
BUN (mmol/L)	6.10$\pm$1.99	6.16$\pm$2.24	0.899
Cr (mmol/L)	79.33$\pm$30.40	87.58$\pm$23.69	0.159
CRP (mg/L)	3.66$\pm$1.02	7.51$\pm$2.30	0.003

3.2. Analysis of plasma levels of omentin-1 and visfatin between the CHD and control group

3.2.1. Analysis of plasma levels of omentin-1 between CHD and control group
Using the t test for independent samples, there was a significant decrease in omentin-1 observed in the CHD group compared to the Control group [(717.63$\pm$229.11) ng/L, (1 115.49$\pm$361.41) ng/L, P=0.000].

3.2.2. Analysis of plasma levels of visfatin between CHD and control group
Using the t test for independent samples, there was a significant increase in visfatin level observed in the CHD group compared to the Control group [(19.22$\pm$6.73 μ g/L, (13.31$\pm$1.69) μ g/L, P=0.002).

3.3. Analysis of plasma levels of omentin-1 and visfatin in SAP, UAP and Control group

3.3.1. Analysis of plasma levels of omentin-1 in SAP, UAP and control group
Using one-way ANOVA test, a significant decrease in omentin-1 was observed in SAP and UAP groups, in contrast with the control group [(780.32$\pm$273.19) ng/L, (1 115.49$\pm$

361.41) ng/L, *P*=0.003; (652.81±152.94) ng/L, (1 115.49± 361.41) ng/L, *P*=0.000]. The plasma levels of omentin–1 in the UAP group were lower than that in the SAP group, but the difference had no statistical significance [(652.81± 152.94) ng/L, (780.32±273.17) ng/L, *P*>0.05].

3.3.2. Analysis of plasma levels of visfatin in SAP, UAP and control group

Using one–way ANOVA test, a significant increase in visfatin was observed in SAP and UAP groups, in contrast with the Control group [(17.92±4.19) μg/L, (13.31±1.69) μg/L, *P*=0.002; (20.43±8.31) μg/L, (13.31±1.69) μg/L, *P*=0.000]. The plasma levels of visfatin in the UAP group were higher compared with the SAP group; however, the difference had no statistical significance [(20.43±8.31) μg/L, (17.92±4.19) μg/L, *P*>0.05].

3.4. Analysis of plasma levels of omentin–1 and visfatin in different NYHA classifications of the CHD group

3.4.1. Analysis of plasma levels of omentin–1 in different NYHA classifications of the CHD group

There were significant increases in omentin–1 levels in (NYHA) functional Ⅰ class group than in functional Ⅱ/Ⅲ class group, functional Ⅳ class group [(1 033.87±277.84) ng/L, (676.58±137.25) ng/L, (540.35±59.49) ng/L, all *P*<0.05]. The plasma levels of omentin–1 in functional Ⅳ class group were significantly decreased compared to that of functional Ⅱ/Ⅲ class group, and the difference had statistical significance [(540.35±59.49) ng/L, (676.58±137.25) ng/L, *P*=0.000].

3.4.2. Analysis of plasma levels of visfatin in different NYHA classifications of the CHD group

There were significant increases in visfatin levels in (NYHA) functional Ⅳ class group than in functional Ⅱ/Ⅲ class group and functional Ⅰ class group [(25.23±11.30) μg/L, (19.08±2.97) μg/L, (13.00±1.19) μg/L, all *P*<0.05]. The plasma levels of visfatin in functional Ⅱ/Ⅲ class group were significantly increased compared to that of the functional Ⅰ class group. The difference had statistical significance [(19.08±2.97) μg/L, (13.00±1.19) μg/L, *P*=0.002].

3.5. Correlations

A significant correlation between lower omentin–1 levels and higher Systolic Pressure (SBP) (*r*=−0.264, *P*<0.05), and lower HDL–c levels (*r*=0.271, *P*<0.05) was observed. We also observed a significant correlation between higher visfatin levels and higher TC levels (*r*=0.292, *P*<0.05), and lower HDL–c levels (*r*=−0.266, *P*<0.05). Lastly, there was also a significant correlation between lower omentin–1 levels and higher visfatin levels (*r*=−0.280, *P*=0.032) (Figure 1).
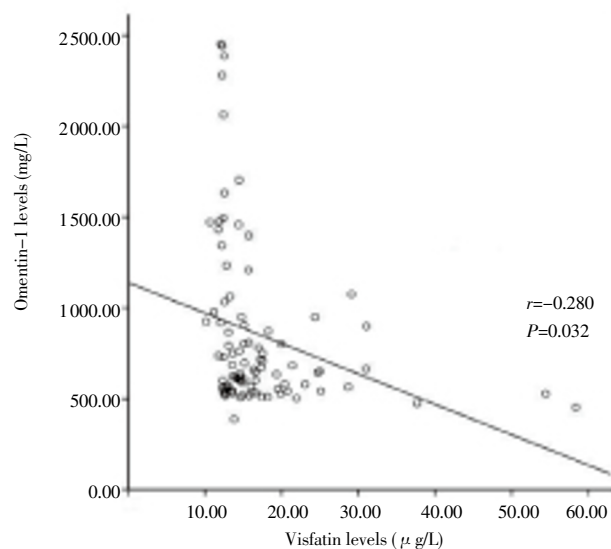

Figure 1. Correlation between omentin–1 and visfatin levels.

3.6. Multiple linear stepwise regression analysis of the factors that influence omentin–1 and visfatin levels

The results of multiple linear stepwise regression analysis demonstrated that plasma levels of omentin–1 was affected by HDL–c levels (*P*=0.006), and the regression equation was $Y=240.100+563.067X_{HDL-c}$; plasma levels of visfatin was affected by HDL–c levels (*P*=0.025), and the regression equation was $Y=25.529-7.720X_{HDL-c}$.

3.7. Logistic regression analysis

As shown in Table 2, logistic regression analysis demonstrated that the risk of CHD was significantly associated with HDL–c (*P*=0.006), CRP (*P*=0.000), and visfatin levels (*P*=0.001).

Table 2
Logistic regression analysis.

Factors	*OR*	*95%CI*	*P*–values
HDL–c	0.007	0.000–0.194	0.003
CRP	2.030	1.387–2.972	0.000
Visfatin	1.948	1.302–2.914	0.001

4. Discussion

4.1. Relations between CHD and omentin–1 levels

The adipokine theory is a widely accepted theory. It suggests that adipocytokines are involved in the inflammatory response, which directly promotes the occurrence of CHD. Omentin–1 was reported to be expressed specifically in omental adipose tissue. Omentin–1 was a new anti–inflammatory cytokine and its anti–inflammatory role was attributed, at least in part, to the inhibition of superoxide

production[3,4]. Omentin mRNA was predominantly found in epicardial and omental adipose tissues[11].

Previous studies[12,13] have demonstrated that omentin levels were lower in patients with CAD compared with controls. Moreover, serum omentin–1 concentrations were independently correlated with CAD. Patients with ACS also had lower serum concentrations of omentin–1 compared with patients with SAP[13]. However, other research[12] suggested that there were no changes in plasma omentin levels in ACS group compared with SAP group. We reported that plasma levels of omentin–1 were significantly lower in patients with CHD compared with controls. Furthermore, there was a decreasing trend in omentin–1 levels in UAP group than SAP group, but the difference had no statistical significance. This result was in accord with the result of previous studies. Consequently, lower omentin–1 levels may be related to the occurrence of CHD.

Further analysis showed that there was a positive correlation between plasma concentrations of omentin–1 and HDL–c levels. Omentin may be involved in the development process of lipid metabolism and AS through the regulation of the phosphorylation of Akt. Initially, omentin may improve insulin sensitivity by increasing the phosphorylation of Akt[14]. Decreased omentin levels have been related with the insulin resistance (IR)[3]. Moreover, hyperinsulinemia induced by IR not only can promote the synthesis of TC in the liver; it can reduce the fat protease activity causing TG decomposition barrier. The elevated levels of TG can hinder the conversion of very low–density lipoprotein (VLDL) into HDL; therefore, VLDL levels increase and HDL–c decrease. Clinical and epidemiological studies have proved that there is a negative correlation between HDL–c levels and CHD incidence rate. Studies[3] also found that there was a negative correlation between omentin–1 levels and HDL–c levels. Moreover, Cai et al[15] found that HDL–c levels were independently correlated with omentin–1 concentrations. Thus, these studies support our results. We speculated that omentin –1 may be a protective factor for CHD. However, the use of lower levels of omentin–1 as an evaluated indicator of risk factors in patients with CHD must be further evaluated, and more clinical studies are needed to confirm these findings.

In addition, Duan et al[16] demonstrated for the first time that omentin can inhibit osteoblastic differentiation of calcifying vascular smooth muscle cells (CVSMCs) via PI3K/Akt signaling pathway. This suggests that the lower omentin levels in obese (specially visceral obese) subjects contribute to the development of arterial calcification, and that omentin plays a protective role against arterial calcification. Xie et al[17] found that omentin–1 ameliorates arterial calcification and bone loss *in vivo* through the regulation of the RANK

signaling pathway. Artery calcification usually occurs on the basis of arteriosclerosis. Elastic fiber degeneration and AS lead to the decline in aortic elasticity, and once the vessel accumulates with arterial calcification, the degree of hardening becomes relatively more serious. With the increase of age, large artery elasticity decreases gradually, and SBP increases while DBP decreases, which lead to the increase in pulse pressure. If combined with arteriolar sclerosis, SBP, and DBP increase. Our results indicate that plasma omentin–1 levels were negatively associated with SBP, which suggests that SBP was higher, omentin–1 level was lower, and the degree of arteriosclerosis may be more substantial. Shibata et al[18] studied a group of male patients with CHD; their results supported the findings of our study. However, to date, there are different opinions regarding coronary artery calcification (CAC). Some studies suggested that CAC was a "bad" phenomenon; others believed that artery calcification could be a protective effect. Thus, it should be elucidated whether omentin has a "beneficial" effect in the development of AS. In addition, there has been little research on the relationship between omentin–1 levels and blood pressure, which also need further study.

El et al[19] reported that TNF– α played a significant role in the pathophysiology of congestive heart failure (CHF). Omentin played an anti–inflammatory role by preventing the TNF– α –induced superoxide or vascular inflammation[20]. Zhong et al[21] found that omentin may inhibit TNF– α –induced expression of adhesion molecules in endothelial cells by blocking the ERK/NF–kappaB pathway. In our study, patients in a higher NYHA class show lower concentrations of omentin–1 than those in a lower NYHA class, which suggest that decreased omentin–1 levels may be associated with the severity of heart failure. Based on these studies, omentin–1 could play an important role in the development of CHD; however, its mechanism is still unclear. We speculate that omentin–1 may inhibit TNF– α –induced expression of vascular cell adhesion molecule–1 (VCAM–1) by blocking the ERK/NF–kappaB pathway to protect CHD patients with heart failure, but this should be studied further.

4.2. Relations between CHD and visfatin levels

Visfatin is another kind of adipocytokine discovered in recent years, which may be associated with obesity, blood glucose metabolism and cardiovascular risk factors. Visfatin proteins were found to be predominantly released by visceral white adipose tissue (WAT) macrophages, and visfatin was considered to be a pro–inflammatory marker[22]. Visfatin is a pro–inflammatory factor, which can increase the expression of TNF– α , interleukin–8 (IL–8), interleukin–6 (IL–6) and

other cytokines, thereby accelerating the development of cardiovascular disease[23]. Ooi *et al*[24] reported that visfatin and its genetic variants were associated with adiposity, obesity–related morbidities and adverse cardiometabolic parameters, which suggest that visfatin played a significant role in the development of obesity–related morbidities and cardiometabolic risk. Dahl *et al*[10] found that visfatin may be an inflammatory mediator, localized in foam cell macrophages within unstable atherosclerotic lesions, which may potentially play a role in plaque destabilization. Previous studies have found that visfatin has a role similar with nicotinamide phosphoribosyltransferase (Nampt), and was formerly known extracellularly as pre–B cell colony–enhancing factor (PBEF), and intracellularly as Nampt. Pillai *et al*[25] found that cardiomyocytes were capable of secreting Nampt during stress, and exogenous Nampt was a positive regulator of cardiac hypertrophy and adverse ventricular remodeling. In addition, visfatin exerts direct cardioprotective effects[26]. Visfatin mRNA expression could be up–regulated in the fat tissue of obesity due to hypoxia[27], which suggest that myocardial ischemia may have up–regulated the expression of visfatin. Hence, present studies are inclined to accept that visfatin levels accelerate the occurrence and development of cardiovascular diseases amidst different opinions about whether visfatin is a protective factor or a pro–inflammatory cytokine in the development of cardiovascular diseases. Plasma visfatin concentrations were increased in participants diagnosed with cardiovascular diseases[28]. Plasma levles of visfatin in patients with CHD were also found to increase significantly compared to that of the control group, and the plasma levels of visfatin in UAP group had an increasing tendency compared with SAP group, but there was no significant difference. Our results suggest that visfatin may be expressed abnormally in patients with CHD, and visfatin may be involved in the occurrence of CHD. However, there seems to be no relationship with the urgent or delayed onset of CHD, which needs to be further studied.

Visfatin was also shown to have insulin–mimetic effects in cultured cells and lowered plasma glucose levels in mice[6]. Yan *et al*[29] found that visfatin could increase insulin sensitivity by up–regulating the levels of peroxisomal proliferator–activated receptor γ (PPARγ) mRNA and insulin receptor substrate–1 (IRS–1) tyrosine phosphorylation, and thus regulated lipid metabolism. Visfatin may regulate cholesterol metabolism in mice by promoting the expression of sterol regulatory element binding protein 2 (SREBP2) and HMG CoA reductase, thus, decrease the cholesterol (including HDL–c) levels[30]. In addition, visfatin perhaps affected TG metabolism through the alteration of one or several genes of dominanting TG

metabolism upstream, and also can regulate the metabolism of cholesterol[31]. Moreover, Sethi *et al*[32] found that visfatin can convert plasma glucose into TG, and promote the accumulation of TG in preadipocytes. Mu *et al*[33] found that visfatin levels were strongly correlated with serum TG levels and LDL–c levels, and negatively correlated with HDL–c levels. In our study, we observed that TC levels and TG levels in CHD group were significantly higher than that of control group and HDL–c levels were significantly lower than that of control group. Moreover, v isfatin levels were strongly positively correlated with serum TC levels, and negatively correlated with HDL–c levels. The result of multiple linear stepwise regression analysis suggested that visfatin levels may be affected by HDL–c levels, and logistic regression analysis showed that visfatin was an independent risk factor of CHD. The abovementioned results suggested that visfatin could be involved in lipid metabolism, which leads to the occurrence of CHD. However, these results had differences with other current research, so further study and verification is needed.

Furthermore, Kim *et al*[34] found that visfatin induced the activation of signal transducer and activator of transcription 3 (STAT3), as characterized by increased tyrosine phosphorylation, nuclear translocation, and DNA–binding activity in human endothelial cells. Visfatin also significantly up–regulated mRNA and protein levels of endothelial interleukin–6 (IL–6). *In vitro*, Liu *et al*[35] demonstrated that visfatin could up–regulate the secretion of MCP–1 and IL–6 in a dose– and time–dependent manner in human umbilical vein endothelial cells. In addition, visfatin–induced MCP–1 and IL–6 production involved p38 MAPK, PI3K, and ERK 1/2 pathways in human umbilical vein endothelial cells as determined by inhibition with specific inhibitors. Another research[36] also found that the levels of serum IL–6 and TNF–α in patients with CHF were significantly increased in comparison with control group, and there were significant differences of serum IL–6 and TNF–α levels among NYHA Ⅱ, Ⅲ and Ⅳ in patients with congestive heart failure (CHF), which suggested that serum IL–6 and TNF–α level might play an important role in pathogenesis of CHF. Thus, we presume that visfatin might up–regulate IL–6 levels by inducing the activation of STAT3, as characterized by increased tyrosine phosphorylation, to participate in the development of CHF. Morever, Kim *et al*[37] found that visfatin was a vascular inflammatory molecule that increases the expression of the inflammatory CAMs, ICAM–1 and VCAM–1, through ROS–dependent NF–κB activation in endothelial cells. Thus, we speculate that visfatin up–regulates VCAM–1 levels through activating ROS–dependent NF–κB, and then participates in the development of CHF. Our study found that visfatin levels

gradually increased with the increase of NYHA grade in patients with CHF, and there were significant differences among NYHA I class, NYHA I Ⅱ/Ⅲ class, NYHA Ⅳ class groups, demonstrating that visfatin might participate the development of CHF, and that the plasma levels of visfatin could reflect the severity of heart function. However, further investigation about this mechanism is needed.

4.3. Relevance between omentin–1 and visfatin levels

Yamawaki *et al*[20] demonstrated that omentin played an anti–inflammatory role by preventing the TNF– α –induced superoxide or vascular inflammation. In addition, omentin may inhibit TNF– α –induced expression of adhesion molecules in endothelial cells by blocking the ERK/NF–kappaB pathway[21]. Morever, visfatin can up–regulate the expression of inflammatory cytokines (such as IL–6, IL–8, MCP–1 and so on). Also, visfatin was a vascular inflammatory molecule that increases the expression of the inflammatory CAMs, ICAM–1 and VCAM–1, through ROS–dependent NF– κ B activation in endothelial cells[37]. Taken together, we speculate that omentin–1 and visfatin regulate the expression of VCAM–1 and IL –6 through different pathways, and then become involved in the development of CHF. Our study found that omentin–1 levels were strongly correlated with visfatin levels in senile CHF, which suggested that omentin–1 and visfatin both played an important role in the development of senile CHF. However, the two roles were reversed, and further evaluation is needed to determine whether there was interaction between omentin–1 and visfatin.

The present study was a cross–sectional study that could only indicate that there was a relationship between omentin–1 levels, visfatin levels and CHD. However, the study could not demonstrate the increase of omentin levels and decrease of visfatin levels were primary or secondary. There were no objective indicators on clinical typing and grading of heart function boundaries. All records were based on the patient´s subjective symptoms. Further research using a larger sample size is needed. The study population was the elderly; thus, there may be other factors that affected the plasma level of omentin –1 and visfatin.

Adipocytokines, especially the omentin–1 and visfatin, have been in the center of research over the recent years. Our study found that omentin–1 and visfatin levels significantly decreased in CHD patients, and omentin–1 levels were negatively associated with SBP and visfatin levels. Moreover, the plasma levels of omentin–1 and visfatin might both be affected by HDL–c levels, and visfatin may be an independent risk factor of CHD. These results provide a basis for the significance of clinical detection of omentin–1

and visfatin levels, and a new initiative for the prevention and treatment of CHD.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Lago F, Dieguez C, Gómez–Reino J, Gualillo O. The emerging role of adipokines as mediators of inflammation and immune responses. *Cytokine & Growth Factor Rev* 2007; **18**(3–4): 313–325.

[2] Yang R, Xu A, Hu JPH, Jadhao S, Hansen B, Shuldiner A, et al. Cloning of omentin, a new adipocytokine from omental fat tissue in humans. *Diabetes* 2003; (Suppl. 1): A1(1–OR).

[3] Yamawaki H, Kuramoto J, Kameshima S, Usui T, Okada M, Hara Y. Omentin, a novel adipocytokine inhibits TNF–induced vascular inflammation in human endothelial cells. *Biochem Biophys Res Commun* 2011; **408**(2): 339–343.

[4] Kazama K, Usui T, Okada M, Hara Y, Yamawaki H. Omentin plays an anti–inflammatory role through inhibition of TNF–alpha–induced superoxide production in vascular smooth muscle cells. *Eur J Pharmacol* 2012; **686**(1–3): 116–123.

[5] Shang FJ, Wang JP, Liu XT, Zheng QS, Xue YS, Wang B, et al. Serum omentin–1 levels are inversely associated with the presence and severity of coronary artery disease in patients with metabolic syndrome. *Biomarkers* 2011; **16**(8): 657–662.

[6] Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science* 2005; **307**(5708): 426–430.

[7] Sonoli SS, Shivprasad S, Prasad CV, Patil AB, Desai PB, Somannavar MS, et al. Visfatin–a review. *Eur Rev Med Pharmacol Sci* 2011; **15**(1): 9–14.

[8] De Luis DA, Gonzalez SM, Conde R, Aller R, Izaola O, Castro MJ, et al. Lack of effect of a moderate hypocaloric diet on visfatin levels in morbid obese patients: relationship with insulin resistance. *Eur Rev Med Pharmacol Sci* 2010; **14**(12): 1031–1036.

[9] Malyszko J, Malyszko JS, Mysliwiec M. Visfatin and endothelial function in dialyzed patients. *Nephrology (Carlton)* 2010; **15**(2): 190–196.

[10] Dahl TB, Yndestad A, Skjelland M, Oie E, Dahl A, Michelsen A, et al. Increased expression of visfatin in macrophages of human unstable carotid and coronary atherosclerosis: possible role in inflammation and plaque destabilization. *Circulation* 2007; **115**(8): 972–980.

[11] Fain JN, Sacks HS, Buehrer B, Bahouth SW, Garrett E, Wolf RY, et al. Identification of omentin mRNA in human epicardial adipose tissue: comparison to omentin in subcutaneous, internal

mammary artery periadventitial and visceral abdominal depots. *Int J Obes (Lond)* 2008; **32**(5): 810–815.

[12]Feng X, Xu Y. Relationship between plasma P–selectin and coronary heart disease. *Chin J Postgraduates Med* 2009; **32**(34).

[13]Zhong X, Zhang HY, Tan H, Zhou, Y, Liu FL, Chen FQ, et al. Association of serum omentin–1 levels with coronary artery disease. *Acta Pharmacol Sin* 2011; **32**(7): 873–878.

[14]Yang RZ, Lee MJ, Hu H, Pray, J, Wu HB, Hansen BC, et al. Identification of omentin as a novel depot–specific adipokine in human adipose tissue: possible role in modulating insulin action. *Am J Physiol Endocrinol Metab* 2006; **290**(6): E1253–E1261.

[15]Cai R, Wei L, Wu H, Bao YQ, Jia WP, Xiang KS. Serum omentin level and related factors in obese and type 2 diabetic patients. *National Med J Chin* 2008; **88**(16): 1096–1099.

[16]Duan XY, Xie PL, Ma YL, Tang SY. Omentin inhibits osteoblastic differentiation of calcifying vascular smooth muscle cells through the PI3K/Akt pathway. *Amino Acids* 2011; **41**(5): 1223–1231.

[17]Xie H, Xie PL, Wu XP, Chen SM, Zhou HD, Yuan LQ, et al. Omentin–1 attenuates arterial calcification and bone loss in osteoprotegerin–deficient mice by inhibition of RANKL expression. *Cardiovasc Res* 2011; **92**(2): 296–306.

[18]Shibata R, Ouchi N, Kikuchi R, Takahashi R, Takeshita K, Kataoka Y, et al. Circulating omentin is associated with coronary artery disease in men. *Atherosclerosis* 2011; **219**(2): 811–814.

[19]El SW, El TL, Meki AR, Abdel, Moneim A. Proinflammatory cytokines, soluble Fas receptor, nitric oxide and angiotensin converting enzyme in congestive heart failure. *Egypt J Immunol* 2005; **12**(1): 39–48.

[20]Yamawaki H, Kuramoto J, Kameshima S, Usui T, Okada M, Hara Y. Omentin, a novel adipocytokine inhibits TNF–induced vascular inflammation in human endothelial cells. *Biochem Biophys Res Commun* 2011; **408**(2): 339–343.

[21]Zhong X, Li X, Liu F, Tan H, Shang D. Omentin inhibits TNF–alpha–induced expression of adhesion molecules in endothelial cells via ERK/NF–kappaB pathway. *Biochem Biophys Res Commun* 2012; **425**(2): 401–406.

[22]Curat CA, Wegner V, Sengenes C, Miranville A, Tonus C, Busse R, et al. Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia* 2006; **49**(4): 744–747.

[23]Leclercq IA, Da Silva Morais A, Schroyen B, Van Hul N, Geerts A. Insulin resistance in hepatocytes and sinusoidal liver cells: Mechanisms and consequences. *J Hepatol* 2007; **47**(1): 142–156.

[24]Ooi SQ, Chan RM, Poh LK, Loke KY, Heng CK, Chan YH, et al. Visfatin and its genetic variants are associated with obesity–related morbidities and cardiometabolic risk in severely obese children. *Pediatr Obes* 2013.

[25]Pillai VB, Sundaresan NR, Kim G, Samant S, Moreno–Vinasco L, Garcia JG, et al. Nampt secreted from cardiomyocytes promotes development of cardiac hypertrophy and adverse ventricular remodeling. *Am J Physiol Heart Circ Physiol* 2013; **304**(3): H415–H426.

[26]Lim SY, Davidson SM, Paramanathan AJ, Smith CC, Yellon DM, Hausenloy DJ. The novel adipocytokine visfatin exerts direct cardioprotective effects. *J Cell Mol Med* 2008; **12**(4): 1395–1403.

[27]Segawa K, Fukuhara A, Hosogai N, Morita K, Okuno Y, Tanaka M, et al. Visfatin in adipocytes is upregulated by hypoxia through HIF1 α –dependent mechanism. *Biochem Biophys Res Comm* 2006; **349**(3): 875–882.

[28]Chang YH, Chang DM, Lin KC, Shin SJ, Lee YJ. Visfatin in overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases: a meta–analysis and systemic review. *Diabetes Metab Res Rev* 2011; **27**(6): 515–527.

[29]Yang Y, Yang G, Li L, Zhang L, Miao ZY, Lu HM. Effects of visfatin on insulin resistance and expression of related genes in rats. *Medical J Chin People's Liberation Army* 2009; **34**(4).

[30]Li R, Yang G, Li L, Sun Q, Liu JL, Shi SC, et al. Effects of plasma visfatin levels on cholesterol metabolism in liver and SREBP–2 in rats. *J Fourth Military Med Univ* 2008; **29**(15): 1382–1384.

[31]Zhang Y, Li L, Yang G, Lu CM. Effects of visfatin down–regulation on lipid metabolism in 3T3–L1 cells and heipal–6 cells. *Chin J Gerontol* 2013; **33**(01): 77–79.

[32]Sethi JK, Vidal–Puig A. Visfatin: the missing link between intra–abdominal obesity and diabetes? *Trends Mol Med* 2005; **11**(8): 344–347.

[33]Mu J, Feng B, Ye Z, Yuan F, Zeng W, Luo Z, et al. Visfatin is related to lipid dysregulation, endothelial dysfunction and atherosclerosis in patients with chronic kidney disease. *J Nephrol* 2011; **24**(2): 177–184.

[34]Kim JY, Bae YH, Bae MK, Kim SR, Park HJ, Wee HJ, et al. Visfatin through STAT3 activation enhances IL–6 expression that promotes endothelial angiogenesis. *Biochim Biophys Acta* 2009; **1793**(11): 1759–1767.

[35]Liu SW, Qiao SB, Yuan JS, Liu DQ. Visfatin stimulates production of monocyte chemotactic protein–1 and interleukin–6 in human vein umbilical endothelial cells. *Horm Metab Res* 2009; **41**(4): 281–286.

[36]Tang FK, Hua N, Lu H, Xiao J, Tang XZ, Qi Z. Effects of bisoprolol on serum interleukin–6 and tumor necrosis factor–alpha level in patients with congestive heart failure. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2008; **24**(12): 1177–1179.

[37]Kim S, Bae Y, Bae S, Choi K, Yoon K, Koo T, et al. Visfatin enhances ICAM–1 and VCAM–1 expression through ROS–dependent NF– κ B activation in endothelial cells. Biochimica etBiophysica *Acta MolCell Res* 2008; **1783**(5): 886–895.