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*Original Article*

# Relationship of osteopontin and renal function with severity of coronary artery lesions

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**Abstract:** Aim: To explore the relationship of plasma osteopontin (OPN) level and renal function with severity of coronary artery lesions. Methods: OPN level and renal function were detected and compared in 210 patients with coronary heart disease (CHD group) and 134 patients without coronary heart disease (control group) to analyze the relationship of osteopontin and renal function with severity of coronary artery lesions. Results: Plasma OPN and creatinine level were significantly higher in CHD group than those in control group ($P<0.01$), and estimated glomerular filtration rate (eGFR) was lower in CHD group than that in control group ($P<0.01$). The proportions of multi-vessel lesion and moderate to severe decreased renal function were higher in patients with high osteopontin than those in patients with low osteopontin ($P<0.05$), and the proportion of multi-vessel lesion was higher in patients with moderate to severe decreased renal function than that in normal renal function ($P<0.05$). Osteopontin and renal failure were the independent risk factors for coronary heart disease. Conclusions: Plasma OPN level is associated with renal failure, both of which are correlated with the severity of coronary artery lesions.

**Keywords:** Osteopontin, renal failure, coronary heart disease, atherosclerosis

## Introduction

Traditional risk factors for coronary artery lesions include age, hypertension, diabetes, etc.; while it has been determined that renal failure is an independent risk factor for cardiovascular diseases in recent years [1]. In addition, many new risk factors for cardiovascular diseases including osteopontin (OPN) [2] are associated potentially with renal function. OPN, a secretary glycosylated phosphoprotein and found widely in bone, kidney and other tissues, is one of the key factors for occurrence and progress of atherosclerosis [3-5], but the relationship with renal function is still unclear [2]. This study is designed to explore the relationship of osteopontin and renal function and the correlation among osteopontin, renal function and coronary artery lesions by detecting plasma osteopontin (OPN) and renal function.

## Materials and methods

### *General data*

210 patients (110 males and 100 females; age: 66.0 ± 9.8 years) were confirmed to have coronary heart disease (CHD) by coronary angiography in our hospital from January 2012 to June 2012. Among them, 70 patients had a history of smoking, 72 patients had diabetes mellitus and 110 patients had hypertension. 134 patients without coronary heart diseases who had a negative result by coronary angiography in the same period were selected (control group). Among them, 74 males and 60 females; age: 65.1 ± 11.5 years; 40 patients with a history of smoking; 36 patients with diabetes mellitus and 60 patients with hypertension. Exclusion criteria: the following patients were excluded: those with a clear bacterial and viral infection; acute and chronic inflammation, immune diseases and chronic connective tissue diseases; malignancy; hemopathy; a history of surgery or trauma within 1 month; known thrombotic diseases; severe anemia and bleeding disorders; severe hepatic and renal failure; receiving emergency percutaneous coronary intervention.

### *Methods*

The clinical history of disease and general information in all patients were recorded in detail,

**Table 1.** Comparison of general information between the two groups ($\bar{X} \pm s$)

| Groups | CHD group n=210 | Control group n=134 | P |
|---|---|---|---|
| Age (years) | 65.96 ± 9.83 | 65.07 ± 11.52 | 0.442 |
| Male (%) | 110 (52.4) | 74 (55.2) | 0.606 |
| History of smoking, n (%) | 70 (33.3) | 40 (29.9) | 0.554 |
| Diabetes, n (%) | 72 (34.3) | 36 (26.9) | 0.148 |
| Hypertension, n (%) | 110 (52.4) | 60 (44.8) | 0.169 |
| Total cholesterol (mmol/l) | 4.07 ± 1.09 | 4.28 ± 0.97 | 0.07 |
| Low density lipoprotein (mmol/l) | 2.38 ± 0.87 | 2.53 ± 0.81 | 0.113 |
| High density lipoprotein (mmol/l) | 1.30 ± 0.27 | 1.48 ± 0.35 | <0.001 |
| Triglycerides (mmol/l) | 1.8 ± 1.4 | 1.5 ± 0.85 | 0.02 |

**Table 2.** Comparison of OPN level and renal function between the two groups ($\bar{X} \pm s$)

| Items | CHD group | Control group | *P* |
|---|---|---|---|
| OPN (ng/ml) | 66.63 ± 10.0 | 53.93 ± 15.31 | <0.001 |
| eGFR (mL/min/1.73 $m^2$) | 118.90 ± 49.54 | 153.02 ± 68.12 | <0.001 |
| Creatinine (μmol/L) | 68.73 ± 52.98 | 51.52 ± 15.89 | <0.001 |

including gender, age, body mass, smoking history, blood pressure and others as well as the data of blood routine examination, biochemical test, etc. Determination of plasma OPN level was performed, and the detailed procedures were as follows: 5 mL venous blood was collected on fasting in the next morning after admission and placed in a 10 mL heparin anticoagulant tube. The specimens were placed immediately into the refrigerator at 4 degrees Celsius after collection, and the assay was completed within one hour. The samples were centrifuged at 4 degrees Celsius (centrifugal radius: 16 cm; 3000 r/min) for 10 min. The plasma was taken and kept in EP tubes, and they wee stored at -80 degrees Celsius for uniform testing in the future. Determination of the plasma OPN level was performed by ELISA method. The kit was from Shanghai Xitang Biotechnology Co., Ltd and was operated strictly based on the instructions. Judkins method was adopted to perform the selective coronary angiography. The optimum multi-position angiography was selected for each vessel. The angiographic results were analyzed by 2 experienced physicians. The selective coronary angiography was taken as the diagnostic basis for coronary heart disease (one or >1 coronary artery stenosis ≥50%). For the patients with coronary heart disease, the simplified MDRD method was used for estimated glomerular filtration rate (eGFR) based on pre-angiography creatinine levels, and the different renal function states were classified on eGFR: moderate renal failure (eGFR <60 mL/(min·1.73 $m^2$), mild renal failure (eGFR 60~90 mL/(min·1.73 $m^2$)) and normal renal function (eGFR ≥90 mL/(min·1.73 $m^2$)). The coronary heart disease group was divided into the single vessel disease (n=98), double vessels disease (n=72) and multi-vessel disease (n=40) based on the number of coronary artery lesions for the degree of stenosis caused by coronary artery disease. The left main coronary stenosis ≥50% was considered to be double vessels disease. The plasma OPN level and the renal function among the three subgroups were compared respectively.

*Statistical analysis*

SPSS 18.0 was used for statistical analysis; measurement data were expressed as mean ± SD ($\bar{X} \pm s$). *t* test was adopted; and after screening the variables with statistical difference, multivariate Logistic regression analysis was used further. Count data was expressed as a percentage. Pearson chi square and continuity-adjusted chi-square test were used for intergroup comparison; *P<0.05* was considered statistically significant.

## Results

*Comparison of general information between the two groups*

High density lipoprotein cholesterol (HDL-c) in coronary heart disease group was significantly lower than that in control group (*P*<0.01), and triglycerides was obviously higher than that in

**Table 3.** Relationship of OPN level and renal function with the number of diseased coronary artery in CHD group

| Groups | Lower OPN group | | Higher OPN group | | P |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Renal function | | | | | |
| Moderate/severe renal failure | 1 | 1.2 | 12 | 9.3 | 0.039 |
| Mild renal failure | 6 | 7.4 | 26 | 20.2 | 0.012 |
| Normal | 74 | 91.4 | | 70.5 | <0.001 |
| Coronary artery disease | | | | | |
| Single-vessel disease | 51 | 63.3 | 47 | 36.4 | <0.001 |
| Double vessels disease | 21 | 25.9 | 51 | 39.5 | 0.043 |
| Multi-vessel disease | 9 | 11.1 | 31 | 24.0 | 0.020 |

**Table 4.** Coronary artery lesions in patients with different renal functions

| Groups | Single-vessel disease | | Double-vessel disease | | Multi-vessel disease | | P |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Moderate to severe renal failure | 2 | 15.4 | 4 | 30.8 | 7 | 53.8 | |
| Mild renal failure | 16 | 50.0 | 10 | 31.3 | 6 | 18.8 | 0.032 |
| Normal renal function | 80 | 48.5 | 58 | 35.2 | 27 | 16.4 | |

**Table 5.** Logistic regression analysis of the risk factors for coronary heart disease

| Relevant factor | β | SE | Wald | P | Exp (β) | 95% CI of Exp (β) |
|---|---|---|---|---|---|---|
| High-density lipoprotein | 1.723 | 0.449 | 14.727 | <0.001 | 5.6 | 2.323~13.5 |
| Triglyceride | -0.243 | 0.123 | 3.913 | 0.048 | 0.784 | 0.616~0.998 |
| OPN | -0.075 | 0.011 | 43.338 | <0.001 | 0.928 | 0.908~0.949 |
| eGFR | 0.006 | 0.002 | 6.716 | 0.01 | 1.006 | 1.002~1.011 |

the control group ($P$<0.05). No statistical difference was found in gender, age, smoking, proportion of CHD patients with hypertension and diabetes, total cholesterol and low-density lipoprotein cholesterol level between the two groups ($P$>0.05) (**Table 1**).

*Comparison of plasma OPN and renal function between the two groups*

OPN and creatinine levels of the CHD group were significantly higher than those of the control group ($P$<0.01), and eGFR of the CHD group was obviously lower than that of the control group. See **Table 2**.

*Relationship of OPN level and renal function with coronary artery disease in CHD group*

The patients were divided into lower OPN group (OPN<61.5) and higher OPN group (OPN≥61.5) by the cut-off point of median OPN (median=61.5 ng/ml). In the high OPN group, the proportion of double vessels disease and multi-vessel disease, moderate to severe renal failure and mild renal failure were higher than those of the lower OPN group, and the proportion of normal renal function and single-vessel disease was lower than that of the lower OPN group ($P$<0.05). See **Table 3** for the details.

*Coronary artery disease in patients with different renal function of the CHD group*

The composition of the number of diseased coronary artery in patients with different renal functions of the three groups were compared, and it was found that the proportion of the multi-vessel disease of the moderate to severe renal failure group increased significantly through the analysis of Fisher exact test ($P$<0.05). See **Table 4** for the details.

*Relationship of renal dysfunction and coronary heart disease*

Multivariable Logistic regression analysis showed that both OPN and renal failure (estimated glomerular filtration rate was decreased) were the independent risk factors for coronary heart disease. High-density lipoprotein was the protective factor for coronary heart disease. See **Table 5**.

## Discussions

In this study we found that OPN level of the CHD group was significantly higher than those of the control group. Previous studies have shown that OPN can promote adhesion and migration of vascular smooth muscle cells and play an important role in atherosclerosis and restenosis after angioplasty [6]. Atherosclerosis is the most common forms of cardiovascular disease, and its pathological changes mainly involve large and medium-sized arteries, showing the lipid's deposition and calcification in the intima. And the formation of vascular intimal calcification in early process is a process similar to bone development, whose key link is the transformation from vascular smooth muscle cells to the osteogenesis cells. Under the condition of the induction (Inflammatory factor, transforming growth factor beta2β and high-density lipoprotein cholesterol, etc.), vascular smooth muscle cells can be transformed into osteogenesis cell which has the function of synthesis and secretion of osteogenesis cells, including OPN. Isoda et al [3] adopted a high cholesterol diet to induce mice, thus building an atherosclerosis model, and the results showed that fatty streak lesions were decreased in OPN-deficient mice after the high cholesterol diet was given; and the fatty streak lesions were significantly aggravated in OPN transgenic mice, indicating that OPN can promote the formation of atherosclerotic plaque. Scatena et al [7] found that OPN in macrophage and foam cells of human aortic atherosclerotic plaques showed a high expression level.

Ohmori et al [5] collected 178 cases who have received routine coronary angiography, 107 cases of coronary heart disease and 71 cases of non coronary heart disease. Results showed that OPN levels in coronary heart disease group was higher than that of the non coronary heart group (616 ± 308 ng/ml vs. 443 ± 237 ng/ml, P<0.001); As OPN levels rose, the number of coronary whose stenosis >50% increased gradually (single lesion 540 ± 293 ng/ml, double branch lesions 615 ± 230 ng/ml, three lesions 758 ± 416 ng/ml). In multivariate analysis, being independent of traditional risk factors, an increase of 100 ng/ml of OPN was significantly associated with coronary heart disease (Odds ratio=1.21, 95% CI: 1.05-1.39). OPN is higher in patients with coronary artery calcification than in without calcification (608 ± 328 ng/ml vs. 490 ± 246 ng/ml, P<0.01), and related to the amount of calcification (r=0.26, P<0.001) [5]. Yan et al [8] divided the 301 patients into two groups according to OPN, which is greater than the median value and less than or equal to the median value. The results showed that the incidence of coronary heart disease was higher in groups of higher OPN level than in groups of lower OPN level, and the level of OPN was obviously related to the severity of coronary heart disease; Multivariate logistic regression analysis confirmed that the group whose OPN greater than the median was four times of less than or equal to its median in increased risk of coronary heart disease. Berezin et al [9] also revealed that elevated OPN in plasma could be considered as an independent predictor of coronary calcification in T2DM patients with known CAD.

A recent study revealed that serum OPN levels were positively associated with arterial stiffness, and with the extent of CAD [10]. It is suggested that OPN levels are significantly correlated with vascular function contributing to the pathogenesis of atherosclerosis in CAD. This study shows that OPN is an independent risk factor for coronary heart disease, so we can detect the coronary heart disease patients with plasma OPN levels, and which can help predict the severity of coronary artery lesions. Those who are in obviously higher OPN level must be alert to severe coronary artery lesions, and should be given further examination and treatment in time.

OPN is not only a growth factor but also a chemotactic factor (CF). As a growth factor, OPN can also simulate glomerular mesangial cell proliferation besides proliferation and migration of vascular smooth cells; OPN can play a role as a chemotactic factor, and interleukin-1, tumor necrosis factor-α and platelet-derived growth factor can all activate protein kinase C; OPN can play a macrophage-derived chemotaxis effect by activating nuclear factor KB and activating OPN gene transcription to increase the OPN expression in T cells, macrophages and a variety of cells, thus causing damage to kidney and other tissues and fibrosis. Basic researches have confirmed that OPN expression level on glomerular and renal tubular epithelial cell increases and increased OPN expression level was associated with macrophage and T cell infiltration, crescent formation

and tubular interstitial fibrosis in antiglomerular basement membrane (GMB) nephritis model in rats. It has been confirmed by a study that OPN mRNA expression in proximal tubule of patients with minimal-change nephrotic syndrome is positively correlated with urinary protein excretion [11]. Yan et al [8] found that plasma OPN concentration was proportional to the severity of renal function damage, indicating that OPN was an independent risk factor of the severity of renal function damage. From the results of the present study, the higher OPN level in CHD patients is, the more severe the severity of renal function damage is, suggesting that OPN level is related to renal function in CHD patients. OPN may cause renal function damage and renal failure by producing an effect of macrophage-derived chemokine. In turn, renal failure may result in an increase of plasma OPN level. Therefore, a vicious circle appears so as to accelerate renal failure and atherosclerotic process.

Coronary atherosclerosis is one of the manifestations of systemic atherosclerosis, and there is a similarity in the pathogenesis between glomerular sclerosis and coronary atherosclerosis. The risk factors such as hypertension and diabetes also cause glomerular sclerosis to result in renal failure while inducing coronary atherosclerosis. The incidence of coronary heart disease in hypertension and diabetic patients with chronic renal failure is significantly higher [12, 13]. In a study by Zhang et al [14], glomerular filtration rate is obviously reduced in patients with severe coronary artery disease. From the results of the present study, the more severe the renal function damage is, the higher the incidence of multi-vessel coronary artery disease is, and renal function is positively correlated with the severity of coronary artery lesion. The results of Logistic regression analysis show that renal failure is a risk factor for coronary heart disease. The population with a high risk for coronary heart disease need have a regular monitoring of renal function, which is beneficial to early identification and diagnosis of coronary heart disease; close monitoring of the changes in renal function should be performed in hospitalized patients, helping preassessment of the severity of coronary artery disease and judgment of disease sequelae.

The results from this study suggest that the plasma OPN level is highly correlated with the severity of renal function damage, that is, the higher OPN level is, the more severe the renal function damage is; both OPN and renal failure are the risk factors for coronary heart disease, which is reflected by the fact that the severity of coronary artery lesion is obviously increased with increase of OPN level or exacerbation of renal function damage. Monitoring of OPN with renal function helps determine the condition and prognosis of coronary heart disease, providing a new idea for the laboratory diagnosis of coronary heart disease.

## Disclosure of conflict of interest

None.

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