High levels of HB-EGF and interleukin-18 are associated with a high risk of in-stent restenosis

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ABSTRACT

Objective: To explore the clinical significance of heparin-binding epidermal growth factor-like growth factor (HB-EGF), interleukin-18 (IL-18), and interleukin-10 (IL-10) in restenosis after percutaneous coronary intervention (PCI).

Methods: A total of 198 patients with acute coronary syndrome underwent coronary drug-eluting stent implantation and were divided into the restenosis group and non-restenosis group on the basis of second coronary angiography. Biological parameters and HB-EGF, IL-18, and IL-10 levels were measured. Patients in the restenosis group were further divided into 3 subgroups according to Gensini score: group A (Gensini score of <20), group B (Gensini score of ≥20 but <40), and group C (Gensini score of ≥40).

Results: Compared with the non-restenosis group, HB-EGF and IL-18 levels were significantly higher but serum IL-10 levels were significantly lower in the restenosis group. Furthermore, HB-EGF levels increased with the Gensini score among the 3 subgroups. Spearman's correlation analysis showed that HB-EGF levels were associated with IL-18 levels and the number of diseased vessels. Multivariate logistic regression analysis showed that diabetes, HB-EGF, and IL-18 were risk factors for restenosis [odds ratio with 95% confidence interval: 3.902 (1.188-4.415), 2.185 (1.103-4.014), and 2.079 (1.208-4.027), respectively].

Conclusion: The present study has demonstrated that HB-EGF may be used to evaluate the severity of restenosis and coronary artery lesion and that inflammatory responses may be involved in the process of restenosis. *(Anatol J Cardiol 2015; 15: 907-12)*

Keywords: HB-EGF, IL-18, IL-10, coronary artery, restenosis

Introduction

Coronary heart disease (CHD), also called as atherosclerotic heart disease, is the end result of the accumulation of atheromatous plaques within the walls of the arteries that supply the myocardium, and it is the leading cause of death worldwide (1). Several experimental and clinical studies have demonstrated that atherosclerosis is the most important cause of CHD, in which lipids adhere and deposit on the arterial walls and induce inflammation and endothelial dysfunction, resulting in the proliferation and migration of vascular smooth muscle cells and eventually intimal hyperplasia (2). Thus, the inflammatory response may play an important role in the pathological changes associated with CHD (3).

Percutaneous coronary intervention (PCI) has been acknowledged as one of the most effective methods for the treatment of CHD; it involves rapid opening of coronary artery stenosis, restoring blood supply, improving ischemia, and reducing the incidence of adverse cardiovascular events. However, several postoperative issues including acute/chronic coronary artery obstruction and restenosis have been proved to significantly attenuate the advantages of PCI. Restenosis can develop within months after PCI (4). The underlying mechanism of this pathology involves endothelial denudation and mechanical injury of the vessel wall, which enhances inflammatory cell recruitment, ultimately driving excessive smooth muscle cell activation and proliferation (5). Importantly, inflammatory responses have been reported to play critical roles in restenosis (6).

Interleukin-18 (IL-18) has been demonstrated to be involved in the formation, progression, and rupture of atheromatous plaques and is a prospective and independent risk factor for CHD (7, 8). Meanwhile, interleukin-10 (IL-10) has been demon-

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strated to be involved in the progression of atherosclerosis and associated with the development of cardiovascular events (9, 10). Further studies have shown that postinjury intimal hyperplasia, macrophage infiltration, and proliferative activity of intima are reduced by treatment with recombinant human IL-10 (10-12). Therefore, an increase in anti-inflammatory factors may decrease intima proliferation after injury and prevent in-stent restenosis.

Heparin-binding epidermal growth factor-like growth factor (HB-EGF), a vascular endothelial cell growth factor, is a mitogen for vascular smooth muscle cells, fibroblasts, and keratinocytes and is involved in the pathophysiological process of atherosclerosis, tumor progression, and smooth muscle hyperplasia (13-15). HB-EGF has been reported to promote intimal hyperplasia and vascular remodeling, and in turn accelerate the progression of atherosclerosis (16, 17). In situ hybridization and immunohistochemical staining has demonstrated high expression of HB-EGF and HB-EGF mRNA in neointima, suggesting that HB-EGF not only plays a role in the proliferation and migration of vascular smooth muscle cells but also promotes restenosis (18).

Thus, in the present study, the clinical value of HB-EGF, IL-18, and IL-10 in restenosis after PCI and the association with coronary in-stent restenosis were investigated to provide information for risk stratification, prognosis evaluation, and early treatment of patients treated with PCI.

Methods

Study design

198 patients with acute coronary syndrome underwent coronary drug-eluting stent implantation and were divided into the restenosis group and non-restenosis group.

Patient population

The clinical protocol was approved by the institutional Medical Ethics Committee and the study was conducted according to the ethical guidelines outlined in the Declaration of Helsinki. All patients were informed about the study and their written consent forms were obtained.

A total of 198 patients with acute coronary syndrome who underwent coronary angiography after coronary stent implantation at the Xiangyang Central Hospital between July 2012 and July 2013 were included in this study. The patients were divided into 2 groups according to the results of coronary angiography: the restenosis group (≥50% diameter stenosis, n=64) and the non-restenosis group (<50% diameter stenosis, n=134). The following patients were excluded: (1) patients with severe cardiac insufficiency, renal insufficiency, myocarditis, malignancy, severe infection, fever, acute pulmonary embolism, pulmonary heart disease, psoriasis, pregnancy, and autoimmune disease that could induce an increase in HB-EGF, IL-18, and IL-10 levels and (2) patients who received anti-inflammatory drugs including steroidal anti-inflammatory analgesics and other steroid medicines. Data including demographic characteristics, medical history, location of vascular stenosis, severity and type of stenosis, location of stent implantation, type of stent, type of balloon, blood flow grade [Thrombolysis in Myocardial Infarction (TIMI)], time of coronary angiography, in-stent restenosis, location of restenosis, de novo stenosis, and second stent implantation were collected. Patients in the restenosis group were classified according to Gensini score (19). Routine blood, hepatorenal function, and blood glucose examinations were performed before coronary angiography.

PCI procedure and angiographic analysis

Premedication with aspirin 100 mg and clopidogrel 75 mg daily was commenced at least 2-3 days before the PCI procedure, and loading doses of aspirin (300 mg) and clopidogrel (450-600 mg) were always given to those who were not premedicated. PCI procedure and domestic rapamycin drug-eluting stent (Shanghai MicroPort Medical, Firebird) implantation were performed using conventional techniques. According to the proximal and distal diameter of the affected vessel, the stent was selected at a ratio of 1:1 and the stent was 3-5 mm longer than the lesion. Procedural success was defined as a residual stenosis of <20% by visual estimation in the presence of TIMI flow grade 3. After the procedure, the patients received clopidogrel 75 mg/day for at least 12 months and aspirin 100 mg/day infinitely. Serial coronary angiography was performed at baseline (before and after intervention) and at 4- or 6-month follow-up. In-stent restenosis was defined as >50% diameter stenosis at follow-up. Coronary angiograms recorded at identical projections that best showed the stenosis at initial and follow-up studies were used for quantitative coronary angiographic analysis by a validated independent core laboratory. The severity of coronary artery stenosis was evaluated in terms of Gensini scores.

Blood samples

For all the included patients, 5 mL of arterial blood was collected from the radial or femoral artery before coronary angiography. The blood was centrifuged for 10 min to collect serum. Plasma was stored at -80°C for further experiments.

Laboratory methods

Levels of HB-EGF (RnD Systems, USA), IL-18 (Bender MedSystems, Vienna, Austria), and IL-10 (Biovision, USA) were measured by enzyme-linked immunosorbent assay. Routine blood examination was performed using blood cell analysis workstation (Sysmex-XE-AlphaN, Japan); hepatorenal function and blood glucose levels were measured using an automatic biochemical analyzer (Aeroset, Abbott, USA).

Statistical analysis

Statistical analyses were performed using SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). When necessary, the chi-square test was performed. Statistical differences between the measured values were analyzed using a 2-tailed Student's

Table 1. Baseline characteristics of the study population

	Restenosis group (n=64)	Non-restenosis group (n=134)	*P
Sex, male/female	48/16	101/33	0.893
Age, years	66.11±10.11	66.62±9.92	0.826
Smoking (%)	51.6	44.1	0.158
Drinking (%)	25	23.1	0.631
Family history of CAD (%)	9.4	8.9	0.324
Hypertension (%)	75.0	79.1	0.376
Dyslipidemia (%)	28.1	26.9	0.258
MI (%)	35.9	38.1	0.561
Diabetes (%)	28.1	10.4	<0.001
LAD (%)	51	49	0.431
CX (%)	19	20	0.564
RCA (%)	30	31	0.376
Average number of stents, sticks	2.05±1.17	2.02±1.13	0.301
Stent diameter, mm	2.85±0.34	2.90±0.32	0.293
Stent length, mm	23.51±6.85	23.57±6.81	0.376
Stent thickness, um	109.71±22.68	107.81±20.52	0.762
Triglyceride, mmol/L	1.74±1.38	1.73±1.01	0.994
Total cholesterol, mmol/L	4.49±1.07	4.14±0.71	0.075
HDL-C, mmol/L	1.21±0.31	1.18±0.28	0.469
LDL-C, mmol/L	2.52±0.64	2.38±0.57	0.432
Creatinine, mmol/L	76.11±19.74	81.47±0.59	0.275
Urea, mmol/L	5.61±1.32	5.84±1.43	0.469
Uric acid, mmol/L	339.98±99.8	334.09±83.1	0.782
HB-EGF, ng/L	258.7±104.5	175.13±88.3	<0.001
IL-18, ng/L	330.6±90.1	204.9±58.8	<0.001
IL-10, ng/L	14.2±4.3	24.7±8.0	<0.001

Values refer to the number of subjects (%) or means ± SD. *unpaired t-test and chi-square test
CAD - coronary artery disease; CX - circumflex artery; HB-EGF - heparin-binding epidermal growth factor-like growth factor; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; IL-10 - interleukin-10; IL-18 - interleukin-18; LAD - left anterior descending artery; MI - myocardial infarction; RCA - right coronary artery

t-test when the distributions of data were normal; otherwise, the Mann-Whitney U test was performed. A binary logistic regression analysis model was established to study the risk factors associated with restenosis. A p value of <0.05 was considered statistically significant. All values are shown as mean ± SD.

Results

As shown in Table 1, compared with the non-restenosis group, the restenosis group tended to have a higher rate of diabetes mellitus (p<0.001). There were no significant differences in other basic characteristics such as gender, age, smoking history, drinking history, hypertension history, hyperlipidemia, myocardial infarction history, treated vessel, stent number, stent diameter, stent length, and stent thickness (all p>0.05). HB-EGF and IL-18 levels were significantly higher but serum IL-10 levels were significantly lower in the restenosis group than in the non-restenosis group (all p<0.05). There were no significant differences between the 2 groups in terms of the levels of creatinine, urea, uric acid, triglyceride, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol (all p>0.05).

Table 2. Spearman's correlations analysis between assessed biomarkers

	HB-EGF	IL-18	IL-10
HB-EGF	-	0.621*	-0.325*
IL-18	0.621*	-	-0.252
IL-10	-0.325*	-0.252	-
Triglyceride	0.241	0.203	0.342
Total cholesterol	0.249	0.265	0.323
HDL-C	-0.024	-0.326	-0.563
LDL-C	0.206	0.238	0.302
Creatinine	0.457	0.703	0.642
Urea	0.283	0.312	0.325
Uric acid	0.411	0.203	0.342
Diabetes	0.149	0.265	0.323
Number of diseased vessels	0.524*	0.326	-0.563

p<0.001; numbers represent Spearman's correlation coefficients R.
HB-EGF - heparin-binding epidermal growth factor-like growth factor; HDL-C - high-density lipoprotein cholesterol; IL-10 - interleukin-10; IL-18 - interleukin-18; LDL-C - low-density lipoprotein cholesterol
*P values P<0.0001 accepted as statistically significant

Table 3. Logistic regression analysis to study risk factors related to restenosis

	B	Wald	P	EXP (B)	95% CI
Diabetes	1.059	9.547	0.002*	3.902	1.188-4.415
HB-EGF	0.908	10.023	0.001*	2.185	1.103-4.014
IL-18	0.817	8.005	0.003*	2.079	1.208-4.027

CI - confidence interval; HB-EGF - heparin-binding epidermal growth factor-like growth factor; IL-18 - interleukin-18

As shown in Table 2, HB-EGF levels were significantly and positively correlated with IL-18 levels and the number of diseased vessels and negatively correlated with IL-10 levels. No other significant correlations among indicators were observed (all p<0.01).

To confirm the relationship among the biomarkers, conventional risk factors, and restenosis, significantly different variables between the 2 groups were selected and analyzed using logistic regression analysis. The variables remaining in the equation were diabetes mellitus, HB-EGF, and IL-18, which were considered as risk factors for restenosis [odds ratio with 95% confidence interval: 3.902 (1.188-4.415), 2.185 (1.103-4.014), and 2.079 (1.208-4.027), respectively] (Table 3).

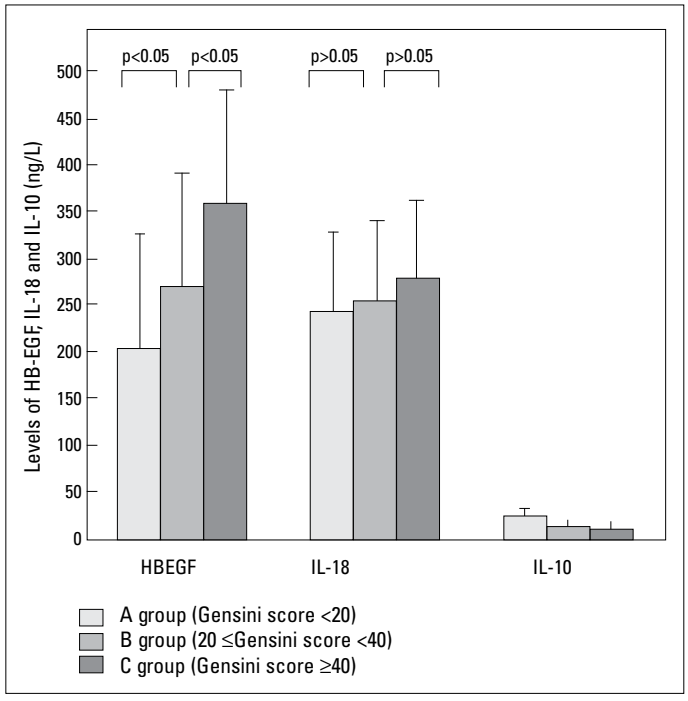

Figure 1. Levels of HB-EGF, IL-18, and IL-10 according to the Gensini score

HB-EGF - heparin-binding epidermal growth factor-like growth factor; IL-18 - interleukin-18; IL-10 - interleukin-10
Mann-Whitney U test was performed.

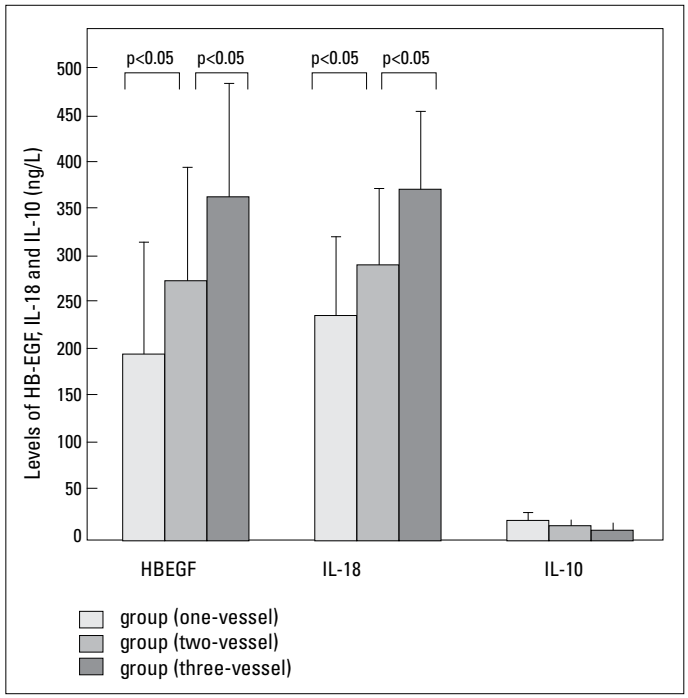

Figure 2. Levels of HB-EGF, IL-18, and IL-10 according to the number of diseased vessels

HB-EGF - heparin-binding epidermal growth factor-like growth factor; IL-18 - interleukin-18; IL-10 - interleukin-10
Mann-Whitney U test was performed.

As shown in Figure 1, HB-EGF levels increased with the Gensini score, whereas IL-18 and IL-10 levels did not differ significantly among the 3 subgroups. As shown in Figure 2, HB-EGF and IL-18 levels in the 1-vessel, 2-vessel, and 3-vessel groups showed a significant difference ($p<0.05$).

Discussion

The present study demonstrated that HB-EGF levels were positively correlated with IL-18 levels and the number of diseased vessels but negatively correlated with IL-10 levels. In addition, IL-18 levels were significantly higher in the restenosis group than in the non-restenosis group, suggesting that inflammatory factors were involved in the process of restenosis. PCI is performed to open the stenosis or occlusion of a coronary artery for improving myocardial perfusion of the patients with CHD and is an important method for the treatment of CHD. However, the subsequent in-stent restenosis remains a challenge for clinicians (20). In-stent restenosis involves a complex process with multiple factors including inflammatory responses, intimal hyperplasia, and vascular remodeling (21). During the process of PCI, a balloon is used to expand the vascular wall of the involved blood vessel before stent implantation; this can result in increased damage to the vascular walls and the response to the injuries can greatly increase the release of tissue factors, which can promote the proliferation of vascular smooth muscle cells and inflammatory cells, induce vascular remodeling and neointimal hyperplasia, and finally result in in-stent restenosis (22). A recent study demonstrated that vascular injuries and inflammatory responses may induce in-stent neointimal hyperplasia (23). Thus, inflammatory responses may play an important role in the process of in-stent neointimal formation. Farb et al. (24) suggested that controlling inflammatory responses should be performed to improve the long-term efficacy of PCI. Libby et al. (25) found that aggregation of leukocytes and platelets at the site of in-stent restenosis is critical in inducing inflammatory responses. Moreno et al. (26) further demonstrated that inflammation may be associated with in-stent restenosis after stent implantation. In addition, the implanted stent can result in continuous stimulation of the vascular wall; induce the release of inflammatory mediators, inflammatory cells, and chronic inflammatory responses of the tunica media; and in turn induce intimal hyperplasia (27). Li et al. (28) found that IL-18 is involved in intimal hyperplasia and migration, proliferation, and diffusion of vascular smooth muscle cells after injuries induced by balloon dilatation, which is in accordance with our findings. In the present study, IL-10 levels were significantly higher in the non-restenosis group than in the restenosis group. Release of anti-inflammatory cytokines is a feedback response to deal with inflammation; imbalance between pro- and anti-inflammatory factors can decrease the anti-inflammatory effects and reduce the inhibition of proliferation and migration of vascular smooth muscle cells, which in turn promote the progression of stenosis. In previous studies, similar to the present study, HB-EGF levels were significantly higher in the restenosis group than in the non-restenosis group and the levels increased with the severity of stenosis, suggesting that HB-EGF, a vascular endothelial growth

factor, can promote the proliferation of smooth muscle cells and affect the process of restenosis. In the present study, we also found that HB-EGF and IL-18 levels were significantly higher in the restenosis group than in the non-restenosis group, and the levels increased with the severity of stenosis; in contrast, the levels of anti-inflammatory factors were considerably lower in the restenosis group than in the non-restenosis group, which is in accordance with the findings of previous studies. These findings suggest that reducing arterial injury and inhibiting inflammatory responses are of great value in reducing intimal hyperplasia.

Intimal hyperplasia at the site of stent implantation is an important factor that can induce in-stent restenosis (29). Proliferation of vascular smooth muscle cells after the destruction of the intima of a coronary artery and damages to the tunica media is critical for the pathological reactions of restenosis, and vascular smooth muscle cells are the main components of the hyperplastic tissues. Asakawa et al. (30) demonstrated that HB-EGF levels were significantly increased when human aortic endothelial cells were cultured with high levels of glucose or in hyperosmolar conditions, suggesting that high glucose levels and hyperosmolarity can increase HB-EGF levels in human aortic endothelial cells and that the microvascular complication of diabetes could be associated with the effects on blood vessels induced by increased HB-EGF levels caused by high blood glucose levels. In the present study, the results of multivariate analysis showed that patients with high HB-EGF levels or with diabetes had an increased risk of in-stent restenosis, which is in accordance with the previous findings.

Study limitations

First, clinical follow-up was limited to 4 or 6 months, and rehospitalization was recorded only if the patients were readmitted to the index hospital. Patients admitted to a different hospital could not be tracked. Second, because of the relatively small sample size, several findings of previous studies could not be confirmed in the present study. Therefore, studies with larger sample sizes are warranted for further investigation. Third, coronary angiography does not provide accurate information about restenosis and CTO or IVUS should be performed in future studies.

Conclusion

First, patients with diabetes or high HB-EGF or IL-18 levels have a high risk of in-stent restenosis; HB-EGF, IL-18, and IL-10 play important roles in the development of in-stent restenosis. Second, HB-EGF levels are positively correlated with IL-18 levels and the number of diseased vessels but negatively correlated with IL-10 levels. Third, diabetes, HB-EGF, and IL-18 are risk factors for in-stent restenosis.

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Peer-review: Externally peer-reviewed.

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