High Plasma Levels of Osteopontin in Patients With Restenosis After Percutaneous Coronary Intervention

To the Editor:

High levels of osteopontin (OPN) mRNA and proteins were reported in atherosclerotic plaques.1,2 Recently, we reported plasma OPN levels to be high in patients with coronary artery disease (CAD) and to correlate with the severity of CAD.3 However, no association between plasma OPN levels and restenosis after percutaneous coronary intervention (PCI) has yet been demonstrated.

We measured plasma OPN levels in 90 patients with CAD undergoing elective coronary angiography for suspected restenosis. They had undergone PCI 0.6±0.4 years ago, of whom 52 (58%) had been treated with bare metal stents. OPN levels were also measured in 60 age- and gender-matched CAD patients with no history of PCI. Patients with acute coronary syndrome were excluded. Our study was approved by institutional ethics committee. After informed consent was obtained, fasting blood samples were taken. Plasma OPN levels were measured by ELISA (Human OPN assay kit; IBL), which measures total concentration of phosphorylated and nonphosphorylated forms of OPN. CAD was defined as at least one coronary artery having >50% luminal diameter stenosis. Restenosis was defined as >50% luminal diameter stenosis in the segment treated by PCI. Differences between 2 groups were evaluated by unpaired t test for parametric variables, by Mann–Whitney U test for nonparametric variables, and by χ² test for categorical variables. A probability value <0.05 was considered significant.

Of the 90 CAD patients with a history of PCI, 42 had restenosis. Compared with 48 CAD patients without restenosis, 42 with restenosis tended to have a higher rate of diabetes and a lower rate of smoking (Table). Among 3 groups, there was no difference in age, gender, or risk factors, except for total cholesterol levels. Plasma OPN levels were higher in CAD patients with restenosis than in those without restenosis and those with no history of PCI (P<0.01; Figure). CAD patients with restenosis more often had OPN level >600 ng/mL than those without restenosis and those with no history of PCI (38% versus 15% and 18%, P<0.05). OPN levels did not correlate with hsCRP, HbA1c, or fasting glucose levels. Clinical variables (age, gender, hypertension, hyperlipidemia, diabetes, smoking, stent, and hsCRP and OPN levels) were entered into multivariate logistic regression model. In addition to diabetes and smoking, OPN levels were independently associated with restenosis. Odds ratio for the presence of restenosis was 1.7 (95% CI=1.2 to 2.5; P<0.01) for a 100 ng/mL increase in OPN levels.

Restenosis after angioplasty is caused by negative arterial remodeling and neointimal proliferation, whereas in-stent restenosis is caused mainly by neointimal proliferation.4 In vitro, OPN promotes the migration and proliferation of smooth muscle cells.5 Increased OPN mRNA was shown in neointimal smooth muscle cells after arterial injury in animal models.1 We generated OPN-overexpressing transgenic mice and demonstrated markedly increased neointimal formation after arterial injury.6 Liaw et al8 showed anti-osteopontin antibody treatment to reduce neointimal formation after injury in rat arteries. In humans, high levels of OPN mRNA and proteins were reported in atherectomy specimens from restenotic lesions.7 Panda et al7 showed plasma OPN levels in 13 patients undergoing coronary atherectomy to be elevated after atherectomy, and they remained high for at least 4 weeks. We showed plasma OPN levels to be higher in patients with than without restenosis and to be an independent factor for restenosis. OPN may play a role in the development of restenosis associated with neointimal proliferation.

Diabetes is a well-known clinical predictor of restenosis. In our study, diabetes was also a factor for restenosis. High glucose increases OPN mRNA in smooth muscle cells.8 Increased OPN expression was shown in diabetic arteries.9 Diabetes may thus facilitate restenosis via increased OPN production. However, OPN levels were a factor for restenosis independent of diabetes. Diabetes and increased OPN production may synergistically facilitate restenosis.

Our study was preliminary, because we did not measure OPN levels before PCI. Further study in a prospective manner is needed to elucidate the predictive value of plasma OPN levels before PCI for the development of restenosis. Moreover, we could not determine the main source of plasma OPN, because we did not measure OPN levels in coronary sinus.
Thus, high plasma levels of OPN in patients with a history of PCI were associated with the presence of restenosis, suggesting that OPN may play a role in the development of restenosis after PCI.

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