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Relationship of interleukin-6-572C/G promoter polymorphism and serum levels to post-percutaneous coronary intervention restenosis

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Background: It has been recently reported that inflammatory mechanisms play an important role in in-stent restenosis (ISR) processes. Inflammatory factors after percutaneous coronary intervention (PCI) for dynamic monitoring can probably predict ISR. Functional polymorphisms in the promoter region of genes coding for inflammatory factors might be important for determining the magnitude of the inflammatory response. Thus, in the present study, we aimed to investigate the serial changes in serum interleukin-6 (IL-6) levels before and after PCI and the relationship between the -572C/G polymorphism in the promoter region of the IL-6 gene and ISR. We also discussed genetic polymorphisms in the inflammatory response to PCI.

Methods: A total of 437 patients who successfully underwent bare metal stent (BMS) implantation with a follow-up angiography were divided into an ISR group (n=166) and a non-ISR (NISR) group (n=271). The IL-6 gene promoter polymorphism at position -572 was determined by restricted fragment length polymorphism using the polymerase chain reaction (PCR-RFLP) method. The serum IL-6 levels before and one day, five days and 180 days after PCI were determined by the radioimmunoassay method.

Results: ISR patients showed higher IL-6 serum levels than NISR patients before PCI ((324.42±28.14) ng/L vs. (283.22±47.30) ng/L, $P<0.001$), and one day post-PCI IL-6 serum levels in the ISR group also showed a significantly higher level than in the NISR group ($P<0.001$). Increased IL-6 after PCI persisted at a statistically significant level throughout the study in ISR patients, whereas IL-6 levels had normalized five days after the procedure in NISR patients. One day post-PCI serum IL-6 level was the most accurate marker for diagnosis of ISR, the area under the ROC curve being 0.927 (95% CI 0.878–0.977). The cut-off value for IL-6 to predict ISR was over 355.50 ng/L, with a sensitivity of 0.968 and a specificity of 0.865. There were no significant differences in frequencies of -572 genotype and allele between the two groups ($P>0.05$). One day post-PCI IL-6 serum levels in patients with the G allele was significantly higher than in patients without the G allele ((366.99±49.37) ng/L vs. (347.20±55.30) ng/L, $P<0.05$). In the ISR group, one day post-PCI serum levels of IL-6 in patients with the G allele was also significantly higher than that in patients without the G allele ((405.67±26.56) ng/L vs. (375.69±38.81) ng/L, $P<0.05$). Multivariate Logistic regression analysis revealed positive correlations between male gender, one day post-PCI serum levels of IL-6, the pre-PCI degree of stenosis, the length of the target lesion stenosis, and restenosis; and there were negative correlations between the stent diameter, the diameter of the reference vessel before stent implantation and restenosis.

Conclusions: IL-6 is an early post-PCI inflammatory cytokine, and one day post-PCI serum IL-6 level is an independent risk factor for restenosis. The frequencies of IL-6 gene -572 genotype and allele are not different between patients with and without ISR in a Chinese Tianjin Han population, but carrying the IL-6 -572G allele is likely to increase an individual's susceptibility to ISR by promoting serum IL-6 levels.

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