MATRIX METALLOPROTEINASES AND THEIR INHIBITORS AND MMP3 POLYMORPHISM IN PERIPHERAL VASCULAR DISEASE

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Aims:Peripheral Vascular Disease (PVD) is a progressive and chronic disease resulting from atherosclerotic events. Atherosclerotic obstructions are consequence of chronic ischemia in the lower extremity arteries in patients with PVD. It is suggested that blood levels of Matrix Metalloproteinases (MMPs) and endogenous Tissue Inhibitors of Metalloproteinases (TIMPs) have been associated with atherosclerosis. On the other hand, MMPs regulate angiogenesis that is a formation of new vessels in atherosclerotic process. In this study, we aimed to demonstrate whether or not levels of MMPs and TIMPs and genetic variations in the matrix metalloproteinase 3 (MMP3) -1171 5A/6A play a role in PVD. Matrix metalloproteinase 3 (MMP3), which is also called Stromelysin-1, is a key member of MMP family and regulate the accumulation of extracellular matrix.

Materials and Methods: The study included 102 patients with PVD (age: 62.78 ± 11.54) and 65 healthy controls (age: 59.66 ± 10.36). The study group were composed from patients which enrolled to the Department of General Surgery, Istanbul University, Istanbul Faculty of Medicine. Serum MMP and TIMP levels were determined by using ELISA method. Genotype analysis was performed for MMP3 5A/6A -1171 5A/6A polymorphism in samples from extraction of DNA using by salting out method from peripheral blood. Polimerase chain reaction (PCR) was performed in DNA samples and then digested amplified DNA with Tth111 I enzyme by using Restriction fragment length polymophism (RFLP). The digested products were separated on a 3 % high resolution agarose gel and visualised using ethidium bromide.

Results: We found that MMP-2 ($p<0.001$), MMP-9 ($p<0.001$) and TIMP-1 ($p<0.01$), TIMP-2 ($p<0.001$) levels in serum were significantly higher in patients with PVD as compared to those of the control group. In PVD group, we found the ratios of MMP-2/TIMP2 and MMP-9/TIMP-2 were increased in PVD group than those of the controls (for both $p<0.001$). In addition, Pearson's correlation test was performed between MMPs and TIMPs levels in patients with PVD group. We found lineer correlation between MMP-2 and TIMP-2 ($r=0.504$ $p=0.000$), and TIMP-1 ($r=0.297$ $p=0.002$). In contrast, we found reverse correlation between MMP-2 and MMP-9 ($r=-0.504$ $p=0.000$). The 5A5A, 6A5A genotypes of MMP3 -1171 5A/6A were more frequent in patients with PVD than in controls. In contrast, 6A6A genotype ($p<0.001$) and 6A allele ($p<0.001$) were significantly decreased in patients as compared with controls.

Conclusions: Our results showed that the changes in the levels of MMPs, TIMPs and the ratios of MMP-2/TIMP2 and MMP-9/TIMP-2 in serum and 6A6A genotype of MMP3 -1171 5A/6A are important in progression of PVD.