

Abstract

Endothelial dysfunction is a pathologic state characterized by an altered equilibrium among vasodilatory and antithrombotic mediators and vasoconstrictive and prothrombotic mediators produced by the vascular endothelium. Multiple factors induce impaired production or increased consumption nitric oxide (NO), the key mediator of vascular homeostasis, produced by the nitric oxide synthase enzymes (NOS). Endothelial dysfunction represents one of the initial steps in the development of atherosclerosis, a chronic inflammatory disease of the vascular wall. The inducible enzyme heme oxygenase 1 (HO-1) represents one of the main cellular defense mechanisms against increased oxidative stress and decreased NO bioavailability accompanying endothelial dysfunction and atherosclerosis. We studied the genetic determinants of endothelial dysfunction and atherosclerosis by evaluating the association of the G894T endothelial NOS (eNOS) polymorphism and the HO-1 (GT)_n promoter polymorphism with coronary artery atherosclerosis severity and risk profile and their evolution during hypolipidaemic treatment. In addition, we searched for genetic variations in exons 25 and 26 of eNOS gene, encoding the C-terminal part of the protein, deemed crucial for proper enzyme function and the 3' - untranslated region crucial for eNOS mRNA stability. We did not find an association of the eNOS G894T polymorphism with the extent and risk profile of coronary atherosclerosis, nevertheless we observed its association with atherosclerotic plaque composition changes during hypolipidaemic therapy. We described a novel variant (G3911A) in the noncoding mRNA of exon 26, a finding warranting further research of its possible impact on eNOS posttranscriptional regulation. The risk HO-1 promoter polymorphism was found to positively correlate with coronary artery atherosclerotic burden and high-risk coronary plaque features.