CILOSTAZOL IMPROVES HIGH GLUCOSE-INDUCED ENDOTHELIAL CELL DYSFUNCTION AND ENHANCES ANGIOGENESIS IN HYPERGLYCEMIC MICE THROUGH ACTIVATION OF AMP-ACTIVATED PROTEIN KINASE PATHWAY

ACC Poster Contributions
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Background: Cilostazol is an antiplatelet agent with vasodilating effect. We and others have reported that it could promote angiogenesis. In this study, we investigated the protective effects of cilostazol in preventing high glucose-induced endothelial cell dysfunction and enhancing angiogenesis in hyperglycemic mice.

Methods: Apoptosis, chemotactic motility and capillary-like tube formation in human umbilical vein endothelial cells (HUVEC) pretreated with high glucose (30 nM) were examined. Phosphorylation of endothelial NO synthase (eNOS), AMP-activated protein kinase (AMPK), and acetyl-coenzyme A carboxylase (ACC) in high glucose-treated HUVEC were performed by immunoblotting. Fifteen-week-old male ICR hyperglycemic mice, induced by streptozotocin injection and high cholesterol diet feeding, were treated intraperitoneally with cilostazol (10 mg/kg) and saline 2 times per day since day 1 to day 7 after hindlimb ischemia and flow recovery in ischemic limb was measured. Quantification of circulating stem cells was performed and capillary density over ischemic limb was examined by counting anti-mouse CD31+ capillaries.

Results: Cilostazol prevented apoptosis, and stimulated chemotactic motility and capillary-like tube formation in high glucose-treated HUVEC as a NO-mediated downstream event through activation of AMPK/ACC-dependent pathways. Blood flow ratio (ipsilateral/contralateral) recovery and capillary density after 21 days in the ischemic hindlimb were significantly improved in cilostazol-treated mice than vehicle control (0.64±0.05 vs 0.33±0.03, p<0.05; 1380±52 vs 1052±26 particles/mm2, p<0.05, respectively) which were attenuated by eNOS inhibitor injection and local AMPK knock down. Circulating CD34+ cells was also significantly higher in cilostazol-treated mice (31.1±9.9 vs 3.2±1.3 cells/ml, p<0.05). Cilostazol increased vascular endothelial growth factor expression, and up-regulated phosphorylation of eNOS, Akt, and AMPK in ischemic muscle.

Conclusions: Cilostazol prevented high glucose-induced endothelial cells dysfunction and enhanced angiogenesis in hyperglycemic mice, partly mediated by activation of eNOS and AMPK pathways.