Abstract: **P722**

**Glycemic control with canagliflozin, a SGLT-2 inhibitor, attenuates atherosclerosis and endothelial dysfunction in diabetic apolipoprotein e-deficient mice**

**Authors:**
A Rahadian¹, D Fukuda², H Salim¹, S Yagi¹, K Kusunose¹, H Yamada¹, T Soeki¹, M Sata¹, ¹Institute of Biomedical Science, Tokushima University Graduate School, Department of Cardiovascular Medicine - Tokushima - Japan, ²Institute of Biomedical Science, Tokushima University Graduate School, Department of Cardio-Diabetes Medicine - Tokushima - Japan,

**Topic(s):**
Atherosclerosis, Cerebrovascular Diseases, Aneurysm, Restenosis

**Citation:**

Background: Canagliflozin is a SGLT-2 inhibitor, a novel type of drug for type 2 diabetes mellitus treatment. Recent studies have shown that SGLT-2 inhibitors reduce cardiovascular events, although the mechanism is still unknown.

Purpose: The aim of our study was to examine the effect of canagliflozin on vascular endothelial cell.

Method: Eight-week-old apolipoprotein E-deficient (ApoE-/-) mice were treated with streptozotocin (STZ, 75 mg/kg/day) in three consecutive days by intraperitoneal injection to induce diabetes. Diabetic ApoE-/− mice were treated with canagliflozin (30 mg/kg/day) by gavage for 12 weeks or 8 weeks to examine its effect on atherosclerosis or endothelial function, respectively.

Results: Canagliflozin significantly decreased blood glucose level (P<0.001), triglyceride level (P<0.05), and total cholesterol level (P<0.05). Sudan IV staining on the aortic arch showed that canagliflozin decreased atherosclerotic lesion progression (P<0.05). Histological analyses using atherosclerotic lesions in the aortic root showed that canagliflozin reduced lipid disposition (P<0.01), macrophage accumulation (P<0.001, and expression of adhesion molecules such as ICAM-1, and VCAM-1 (P<0.01, and P<0.05 respectively). Canagliflozin also attenuated the development of endothelial dysfunction as determined by acetylcholine-dependent vasodilation (P<0.05), and reduced the expression of inflammatory molecules, such as ICAM-1 and VCAM-1 (P<0.01), also MCP-1, F4/80, IL6, and iNOS (P<0.05) in the aorta. Canagliflozin reduced oxidative stress as determined by the reduction of the expression of NOX2, NOX4, p22phox, p47phox in the aorta and by the urinary excretion of 8-OHdG. In vitro experiment using human umbilical vein endothelial cells (HUVEC), methylglyoxal (MGO), a precursor of advanced glycation end products, significantly increased the expression of inflammatory molecules such as ICAM-1, MCP-1, and p22phox in (P<0.05, respectively). MGO also decreased the phosphorylation of eNOSser1177 and Akt, and increased phosphorylation of P38 MAPK in HUVEC.

Conclusion: Glucose lowering effect by canagliflozin attenuates the development of endothelial dysfunction and atherogenesis in diabetic ApoE-/− mice. Anti-inflammatory effect due to the reduction of glucose toxicity on endothelial cells might be one of the mechanisms.