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Empagliflozin, a SGLT2 inhibitor, attenuates endothelial dysfunction and atherogenesis by inhibiting inflammatory responses in the vasculature and adipose tissue in diabetic apolipoprotein E-deficient

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Background: Inflammation and oxidative stress associated with hyperglycemia are major causes of vascular dysfunction and cardiovascular complications in diabetes. Recent studies reported that cardioprotective effects of sodium glucose co-transporter 2 (SGLT2) inhibitors, however underlying mechanisms are still obscure.

Purpose: The aim of this study was to investigate whether empagliflozin attenuates atherogenesis and endothelial dysfunction in diabetic apolipoprotein E-deficient (ApoE-/-) mice and investigated underlying mechanisms.

Methods: ApoE-/- mice were injected with streptozotocin (75 mg/kg) for 3 consecutive days. One week after last injection, a western type diet and administration of empagliflozin (20 mg/kg/day) or vehicle via oral gavage were started. Atherosclerotic plaque area was examined by en face Sudan IV staining. Lipid deposition and inflammatory features of atherosclerotic plaques was examined on lesions in the aortic root by immunohistochemical analysis. Vascular function was assessed by isometric tension recording. mRNA or protein expression level was examined by quantitative RT-PCR (qPCR) or western blot analysis, respectively. In in vitro experiments, murine macrophage cell line, RAW264.7, was used.

Results: Treatment with empagliflozin for 12 weeks significantly decreased atherosclerotic plaque size in the aortic arch compared with untreated group (p<0.01). Empagliflozin reduced blood glucose (p<0.001) and plasma lipid levels. Results of histological analyses revealed that empagliflozin decreased lipid deposition, macrophage accumulation, and the expression of inflammatory molecules in the aortic root. Empagliflozin treatment for 8 weeks significantly attenuated endothelial dysfunction as determined by vascular response to acetylcholine. qPCR results demonstrated that empagliflozin reduced the expression of inflammatory molecules such as MCP-1 (p<0.05), ICAM-1 (p<0.05) and Nox-2 (p<0.05), a major NADPH oxidase subunit, in the aorta compared with the untreated group. Furthermore, empagliflozin significantly mitigated the expression of these inflammatory molecules in fat tissues around the aortic arch as determined by qPCR. In in vitro studies, methylglyoxal (MGO), a precursor of AGEs, increased the expression of inflammatory molecules (e.g., MCP-1, IL-1β and TNF-α (p<0.05, respectively)) in RAW264.7 cells. MGO also significantly induced activation of JNK and p38 MAP kinase (p<0.001, respectively) in this cell-type.

Conclusions: Empagliflozin attenuated endothelial dysfunction and atherogenesis in diabetic ApoE-/- mice. Reduction of inflammation in the vasculature and peri-vascular adipose tissues may have a role as underlying mechanisms at least partially.