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Improved Lipotoxicity by Fenofibrate Ameliorates Diabetic Nephropathy by Attenuating Lymphatic Proliferation in db/db Mice

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Objectives : In diabetic nephropathy, the proliferation of lymphatic vessels correlates with the extent of intrarenal inflammatory cell infiltration and tubulointerstitial fibrosis, which result from hyperglycemic and lipotoxic conditions. Peroxisome proliferative-activated receptor (PPAR) , a lipid-sensing transcription factor, plays an important role against lipotoxicity under the control of AMP-activated protein kinase (AMPK). We evaluated whether fenofibrate, a PPAR agonist, has a renoprotective effect by ameliorating lipotoxicity and lymphangiogenesis in the kidney.

Methods : Eight-week-old male C57BLKS/J db/m and db/db mice were fed fenofibrate for 12 weeks. They were then sacrificed and their biochemical parameters and renal phenotypes were evaluated.

Results : In db/db mice, fenofibrate ameliorated albuminuria, mesangial area expansion, and inflammatory cell infiltration. Fenofibrate inhibited the accumulation of intra-renal free fatty acid and triglycerides, which was associated with increase in the expression of PPAR , phosphorylation of AMPK, activation of PPARγ co-activator 1α-phosphorylated acetyl-CoA carboxylase, and suppression of sterol regulatory element-binding protein 1 (SREBP-1) and carbohydrate regulatory element-binding protein 1 (ChREBP). Fenofibrate decreased lymphatic growth, as represented by decreases in the expression of lymphatic endothelial hyaluronan receptor-1 (LYVE-1) and podoplanin, along with decreases in vascular endothelial growth factor-C (VEGF-C) and vascular endothelial growth factor receptor-3 (VEGFR-3). Consequently, fenofibrate reversed renal apoptosis and oxidative stress, as reflected by urinary 8-hydroxy-deoxyguanosine and isoprostane concentrations. In cultured HK2 cells, fenofibrate prevented palmitate- and high glucose-induced expression of VEGF-C, VEGFR-3, and LYVE-1 via activation of PPAR-AMPK-pACC signaling and suppression of SREBP-1 and ChREBP.

Conclusions : The results suggested that fenofibrate prevents diabetic nephropathy in db/db mice by attenuating lymphatic proliferation through

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PPAR -AMPK pathway, associated with improvement in lipotoxicity-related renal inflammation and fibrosis in the kidney, especially in the proximal tubule cells.

Keywords : Diabetic nephropathy, Fenofibrate, Lipotoxicity, Lymphatics