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Effects of xanthine oxidase inhibitor on cholesterol accumulation related renal injury in chronic kidney disease

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Objectives: Hypercholesterolemia is an important risk factor and associated with the rapid progression of chronic kidney disease (CKD). The effect of topiroxostat (Top), non-purine, and selective xanthine oxidase inhibitor, on renal injury in CKD models with hypercholesterolemia has not been evaluated. In this study, we investigated the effect of TOP on cholesterol accumulation, renal dysfunction, and histologic alterations in uninephrectomized (UNx) ApoE knockout (KO) mice.

Methods: Male ApoE KO (8-week-old) mice (n = 28) were fed a 1.25% cholesterol-containing diet for 12 weeks. Four groups were studied: sham + vehicle (SV) (n = 6); sham + Top (ST) (n=6); UNx+ vehicle (UV) (n = 8) and UNx+Top (UT) (n = 8). Top (1 mg/kg/day, oral gavage) was administered for 4 weeks before end experiment.

Results: Uninephrectomy markedly increased serum cholesterol and kidney injury factor (creatinine and BUN) levels in Apoe KO mice. TOP reduced intracellular ROS production, cholesterol accumulation and increased cholesterol efflux related mRNA and protein expression. Also, TOP regulated autophagy related gene and reduced fibrosis marker gene (Collagen, Fibronectin etc.) expression in kidney.

Conclusions: Top attenuates renal fibrosis by reduced oxidative stress and cholesterol accumulation in renal injury model with hypercholesterolemia.