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Effects of topiroxostat on renal fibrosis in chronic renal failure with hypercholesterolemia.

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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 fibrosis in CKD models with hypercholesterolemia has not been elucidated. The objective of this study was to evaluate the effect of TOP on oxidative stress, 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 (S) +vehicle (V) (n = 6); S+TOP (n = 6); UNx+V (n = 8) and UNx+TOP (n = 8). TOP (1 mg/kg/day, oral gavage) were administered for 4 weeks before end experiment. The levels of serum urea nitrogen (BUN), creatinine, uric acid, and total cholesterol were determined. For investigating renal histology change, trichrome, periodic acid-Schiff (PAS) staining and cellular cholesterol staining were evaluated. Renal gene expression, XOR activity, and oxidative stress were evaluated.

Results: Serum creatinine levels, serum uric acid, total cholesterol were significantly attenuated and oxidative stress was reduced in the kidneys of the S-TOP and UNx-TOP groups compared with the vehicle group. Immunohistochemistry and RT-PCR analysis also showed that TOP reduced cytokeratin, fibronectin and NOX4 expression and attenuated tubulointerstitial fibrosis and cholesterol accumulation in kidney tissue.

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