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Combination therapy with Lisinopril and Dapagliflozin rescues GFR decline and glomerular damage in the KKAy mouse model of diabetic kidney disease

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Background and Aims: Male KKAy mice develop diabetic kidney disease (DKD) with progressive decline of GFR upon high fat diet feeding which is accelerated by the vasoconstrictor LNNA. In this study, efficacy of combination therapy with clinical relevant therapeutics in the form of an ACE-inhibitor (Lisinopril) and SGLT2-inhibitor (Dapagliflozin) on renal function and histopathology was investigated.

Method: Male KKAy mice underwent uninephrectomy (UNX). After recovery mice received high fat diet (45% LARD) and 50 mg/L LNNA in drinking water (wk0). At week 4, Lisinopril (2.5 mg/kg/day in drinking water) and at week 8 Dapagliflozin (5 and 20 mg/kg/day in diet) were started. Body weight, blood glucose, food and water intake and albuminuria were determined regularly. GFR was measured transdermally by FITC-sinistrin clearance. Mice were terminated at week 16 and renal histology was scored by a team of renal histopathologists. Non-induced and induced non-treated mice were used as controls.

Results: Treatment of KKAy mice on HFD+LNNA with Dapagliflozin reduced blood glucose immediately. Combination therapy with Lisinopril and Dapagliflozin (5 mg/kg/day) rescued the progressive GFR decline to levels seen in non-induced chow-controls (p < 0.05 vs UNX+HFD+LNNA). Pathology showed that the percentage of healthy glomeruli increased from 14% to 26% after combination therapy (Dapa 5). Interstitial fibrosis and tubular atrophy were significantly reduced by combination therapy (p < 0.05 vs UNX+HFD+LNNA).

Conclusion: Male KKAy mice on a HFD and LNNA developed DKD resulting in CKD. Combination therapy with Lisinopril and Dapagliflozin rescued GFR decline and reduced glomerular damage and interstitial fibrosis and tubular atrophy. This indicates the clinical relevance of the model which can be used to study compound efficacy in both early and more advanced stages of DKD.