Combination therapy with Lisinopril and Dapagliflozin rescues GFR decline and glomerular damage in the advanced DKD/CKD KKAY mouse model

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Introduction

The prevalence of diabetic kidney disease is rapidly increasing. Development of novel therapeutics is hampered by the lack of translational animal models resembling all stages of DKD. TNO developed a diet-induced hypertension-accelerated DKD model which can be used understand the different disease stages, lead to identification of new therapeutic targets and biomarkers. Response to standard-of-care (SOC) therapy will indicate usability of the model for efficacy studies.

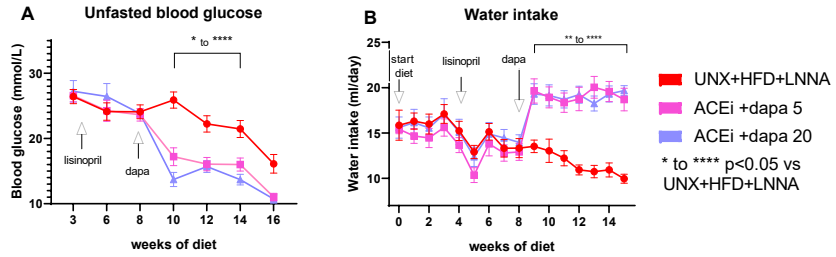
Aim

The aim of this study was to determine efficacy of standard-of-care combination therapy of initial low dose Lisinopril treatment followed by on-top-off Dapagliflozin treatment on renal function and histopathology.

Method

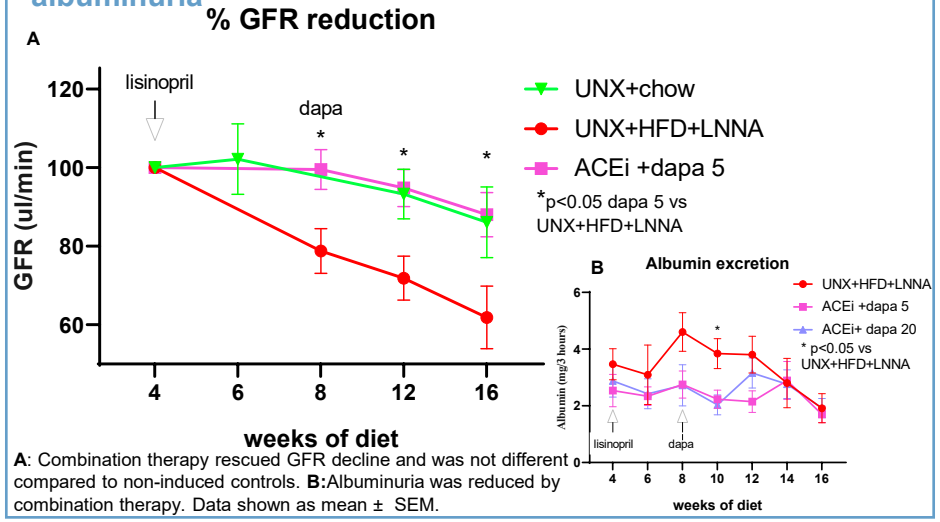
- Male KKAy mice underwent uninephrectomy (UNX). After recovery, mice received high fat diet (HFD) and the vasoconstrictor LNNA (50mg/L) for 16 weeks. At wk 4 Lisinopril (2.5 mg/kg/day) was started. At week 8 Dapagliflozin (5 and 20 mg/kg/day).
- Body weight, food and water intake was monitored weekly, blood glucose every 4 weeks.
- GFR was measured using a transdermal GFR Measurement system.
- Pathology assessment includes quantitatively scoring of glomerular and tubular damage by a team of renal pathologists, GBM thickening by EM microscopy and automated mesangium expansion using image analysis.

Dapagliflozin reduces blood glucose and increases water intake



A: Dapagliflozin immediately reduced unfasted blood glucose levels dose-independently. **B:** Dapagliflozin increased water intake dose-independently. Data shown as mean ± SEM.

Combination therapy rescues GFR decline and reduces albuminuria



A: Combination therapy rescued GFR decline and was not different compared to non-induced controls. **B:**Albuminuria was reduced by combination therapy. Data shown as mean ± SEM.

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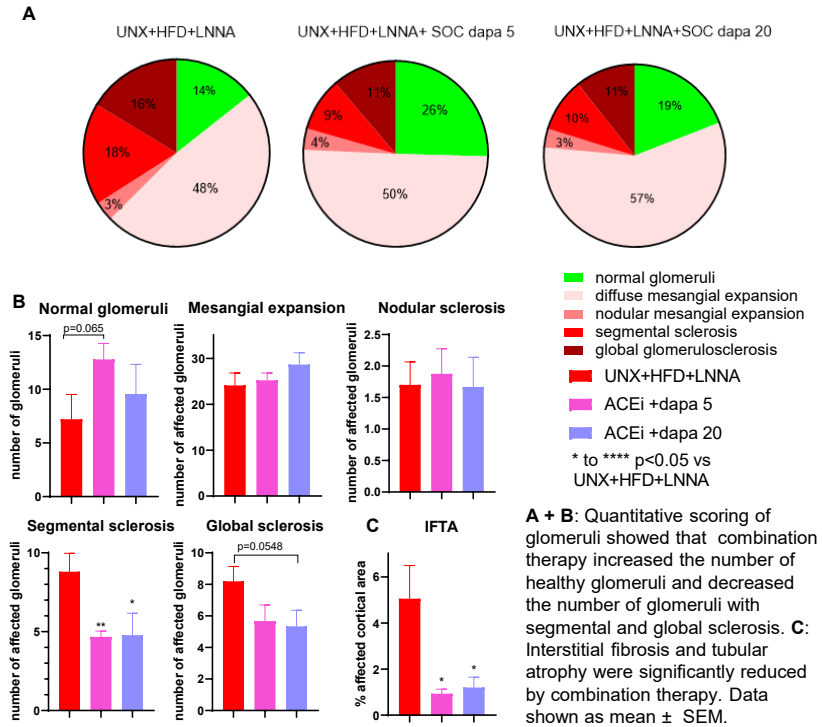
Combination therapy reduces renal damage



A + B: Quantitative scoring of glomeruli showed that combination therapy increased the number of healthy glomeruli and decreased the number of glomeruli with segmental and global sclerosis. **C**: Interstitial fibrosis and tubular atrophy were significantly reduced by combination therapy. Data shown as mean ± SEM.

Conclusions

Combination therapy with a low dose of Lisinopril and Dapagliflozin (5 mg/kg/day) rescues GFR decline and prevents increase of albuminuria in the KKAy DKD/CKD mouse model. Glomerular and tubular damage were reduced by standard-of-care combination therapy. This further supports the usability of the KKAy DKD/CKD mouse model for efficacy studies.

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