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 mesangial expansion using image analysis.

Combination therapy reduces GFR decline and reduces albuminuria

Combination therapy rescues GFR decline and reduces albuminuria

A

% GFR reduction

B

Dapagliflozin reduces blood glucose and increases water intake

A

Unfasted blood glucose

B

Water intake

Combination therapy reduces renal damage

Combination therapy reduces renal damage

A

Normal glomeruli

Mesangial expansion

Nodular sclerosis

B

Segmental sclerosis

Global sclerosis

C

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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.