Standard-of-care combination therapy rescues GFR decline and cardiac damage in a novel cardiovascular-kidney-metabolic syndrome mouse model

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Introduction

Cardiovascular-Kidney-Metabolic (CKM) Syndrome is a complex disorder involving CVD, kidney disease, type 2 diabetes and obesity. These conditions share risk factors and can exacerbate each other. Development of new therapies is hampered by the lack of translational models. A novel diet-induced hypertension-accelerated mouse model with obesity, diabetes and hypertension was developed which shows diabetic and chronic kidney disease (DKD/CKD) and heart failure with preserved ejection fraction (HFpEF).

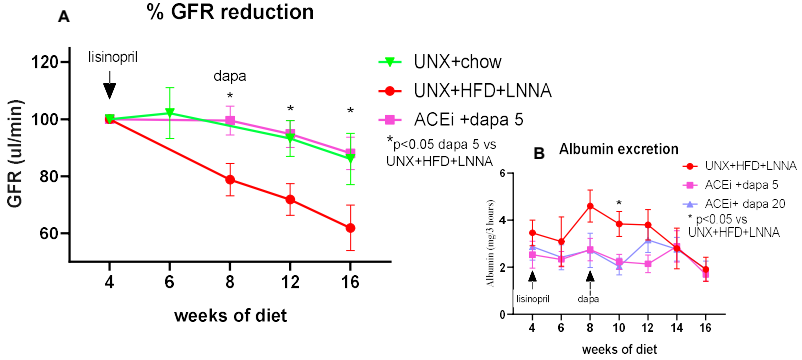
Aim

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 renal and cardiac histopathology.

Method

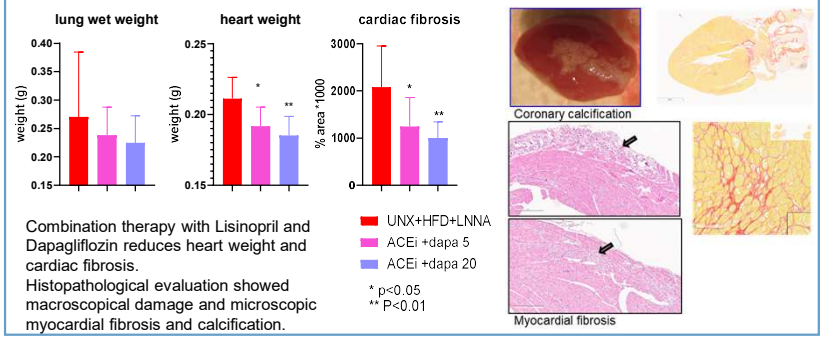
- Male KKAy mice underwent uninephrectomy (UNX). After recovery, mice received high fat diet (HFD) and the vasoconstrictor LNNA (50mg/L) for 16 weeks. At wk 4 Lisinopril (2.5 mg/kg/day) was started. At week 8 Dapagliflozin (5 and 20 mg/kg/day).
- Body weight, food and water intake was monitored weekly, 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.

Combination therapy rescues renal function



Combination therapy rescued GFR decline **(A)** and reduces albuminuria **(B)**. Data shown as mean ± SEM.

Combination therapy reduces cardiac damage



Combination therapy with Lisinopril and Dapagliflozin reduces heart weight and cardiac fibrosis.
Histopathological evaluation showed macroscopical damage and microscopic myocardial fibrosis and calcification.

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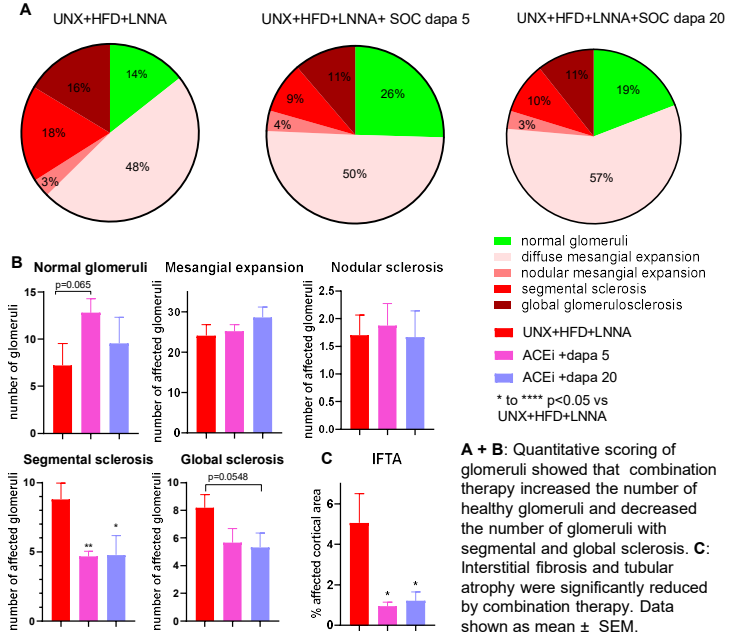
Combination therapy reduces renal damage



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

Male KKAy mice on HFD and LNNA developed DKD resulting in CKD and HFpEF. Combination therapy with Lisinopril and Dapagliflozin rescued GFR decline and reduced renal and cardiac damage. This indicates the clinal relevance of the model allowing holistic and mechanistic studies in both early and more advanced stages of CKM syndrome.