

A novel translational model of hypertension-accelerated diet-induced diabetic kidney disease with declining GFR and advanced pathology

Arienne van Koppen¹, Matt Breyer², Romer Gonzalez Villalobos², Andrea R. Nawrocki², Savithri Kota², Simon Hinke², Tri Q. Nguyen³, Amelie Dendooven⁴, Harry van Goor⁵, Karen Tseng⁶, Wei-Chan Hsu⁶, Aswin Menke¹, Reinout Stoop¹

¹ Department of Metabolic Health Research, TNO Leiden, The Netherlands. ² Janssen Pharmaceuticals, Boston, United States ³ UMCU, Utrecht, The Netherlands. ⁴ UZA, Antwerp and UZ Ghent, Belgium. ⁵ UMCG Groningen, The Netherlands. ⁶ BPM, Taiwan.

TNO innovation for life

Introduction

The prevalence of diabetes and diabetic kidney disease is rapidly increasing. Development of novel therapeutics is hampered by the lack of translational animal models resembling the later stages of the DKD. TNO has developed a diet-induced hypertension-accelerated DKD model. This can help to better understand the different disease stages, lead to identification of new therapeutic targets and biomarkers.

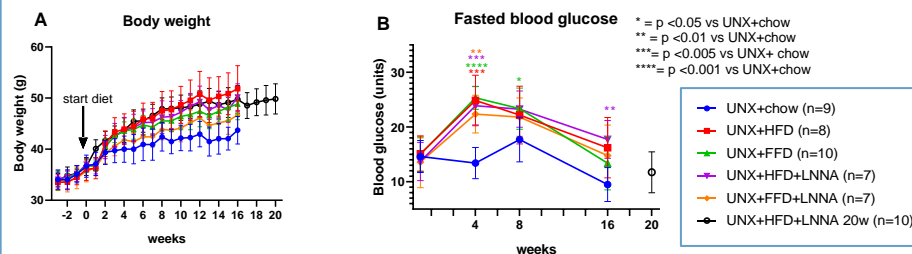
Aim

The aim of this study was to determine the time-dependent progression of the diet-induced DKD model and to evaluate the effect of diet and hypertension functionally and pathophysiologically.

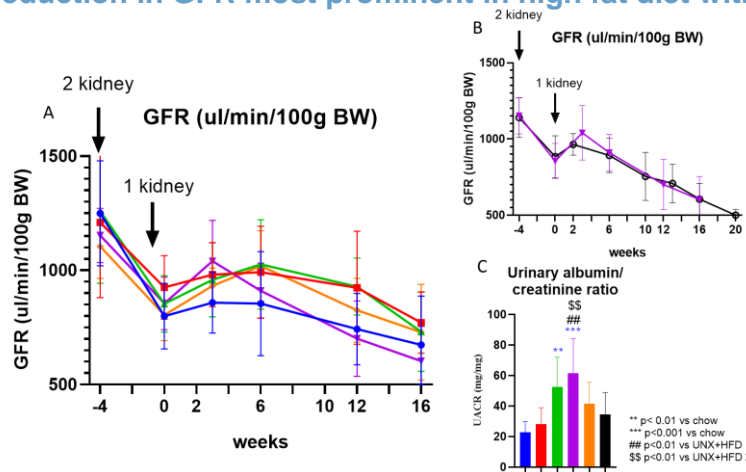
Method

- Male KKAy mice (8 weeks) underwent uninephrectomy (UNX). After 3 weeks recovery, mice received either high fat diet (HFD) or fast food diet (FFD) with or without LNNA (50mg/L) for 16 weeks. Chow-fed mice were used as controls. One group fed HFD+LNNA was continued until week 20.
- Body weight, food and water intake was monitored weekly, blood glucose every 4 weeks.
- GFR was measured transdermally using retro-orbital injections with FITC-sinistrin.
- 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.

HFD and FFD induce comparable diabetes development

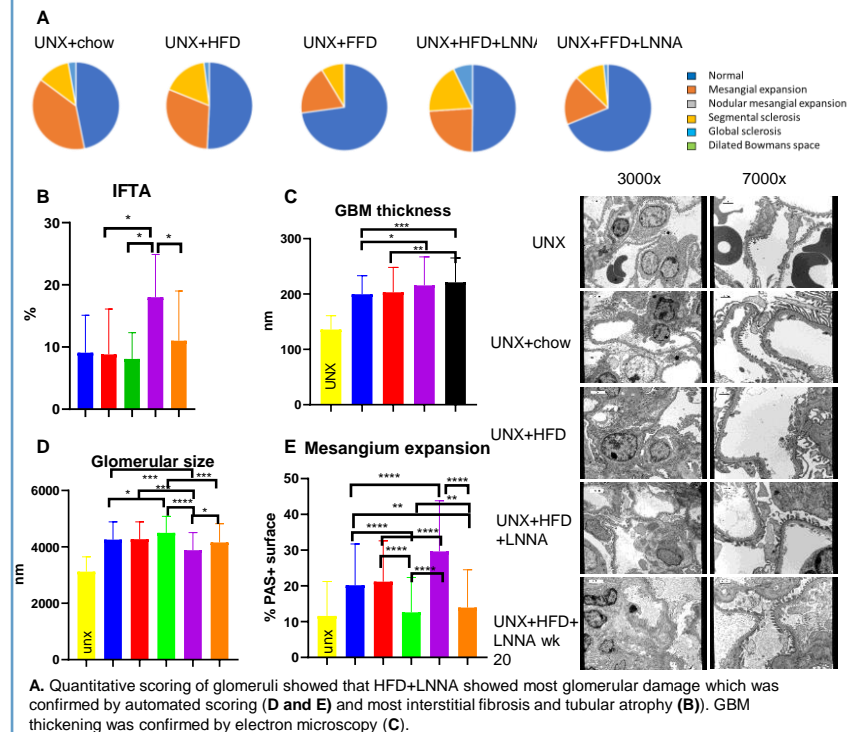


Reduction in GFR most prominent in high fat diet with LNNA



Contact information: arienne.vankoppen@tno.nl

Quantitative sclerosis scoring and GBM thickening



Conclusions

DKD development was most prominent in male KKAy mice on HFD and LNNA (50 mg/L) as shown by an initial period of hyperfiltration followed by a continuous decline of GFR and advanced renal pathology. Together with increased albuminuria this indicates that the mice reach the phase of overt DKD resembling the clinical phenotype.