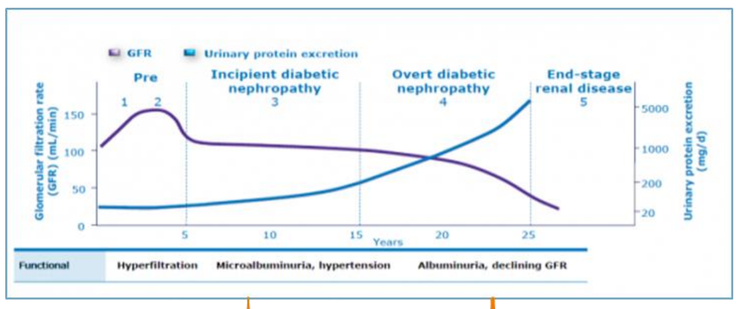
A MOUSE MODEL OF MODERATE DIABETIC NEPHROPATHY ON A METABOLIC SYNDROME BACKGROUND

Arianne van Koppen
Christa de Ruiter
Joline Attema
Reinout Stoop

TNO Metabolic Health Research
Leiden, the Netherlands

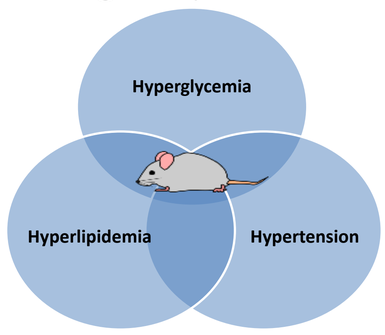
Introduction

Diabetic nephropathy (DN) is the main cause of end stage renal disease and a major complication in metabolic syndrome and diabetes. We aim to develop a translational DN mouse model on metabolic syndrome background by incorporating the three main features of DN including hyperglycemia, hyperlipidemia and hypertension. This model will help to identify key processes involved in disease development and progression and guide preclinical research.



Aim

- Develop a translational mouse model of moderate DN by combining key features of human DN.



Methods

Experimental design:

-1	0 wk	14 wk
UNX	chow	
UNX	High Fat Diet (HFD)	
UNX	HFD + Pro-Hypertensive (HFD + pro-hyp)	

Readouts:

- Body weight
- Blood glucose & insulin
- Blood pressure
- GFR by inulin clearance
- Morphology

Looking for partners!

Key feature selection experiment
Goal: Define the time for HFD feeding and dissect the additive effect of hypertension

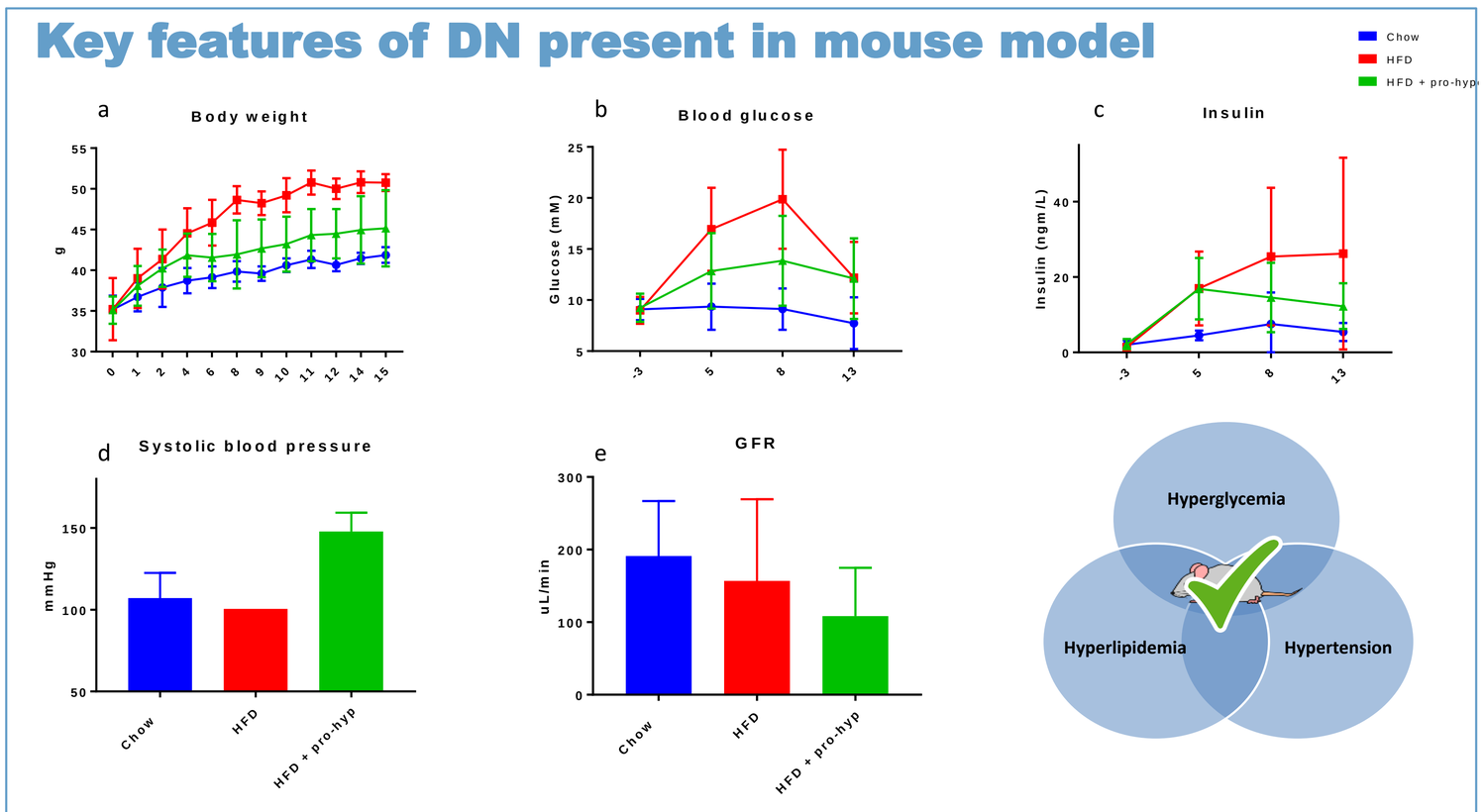
↓

Time course experiment
Goal: Generate insight in temporal dynamics of key processes in disease onset and progression
Define stage-related/process related signatures

↓

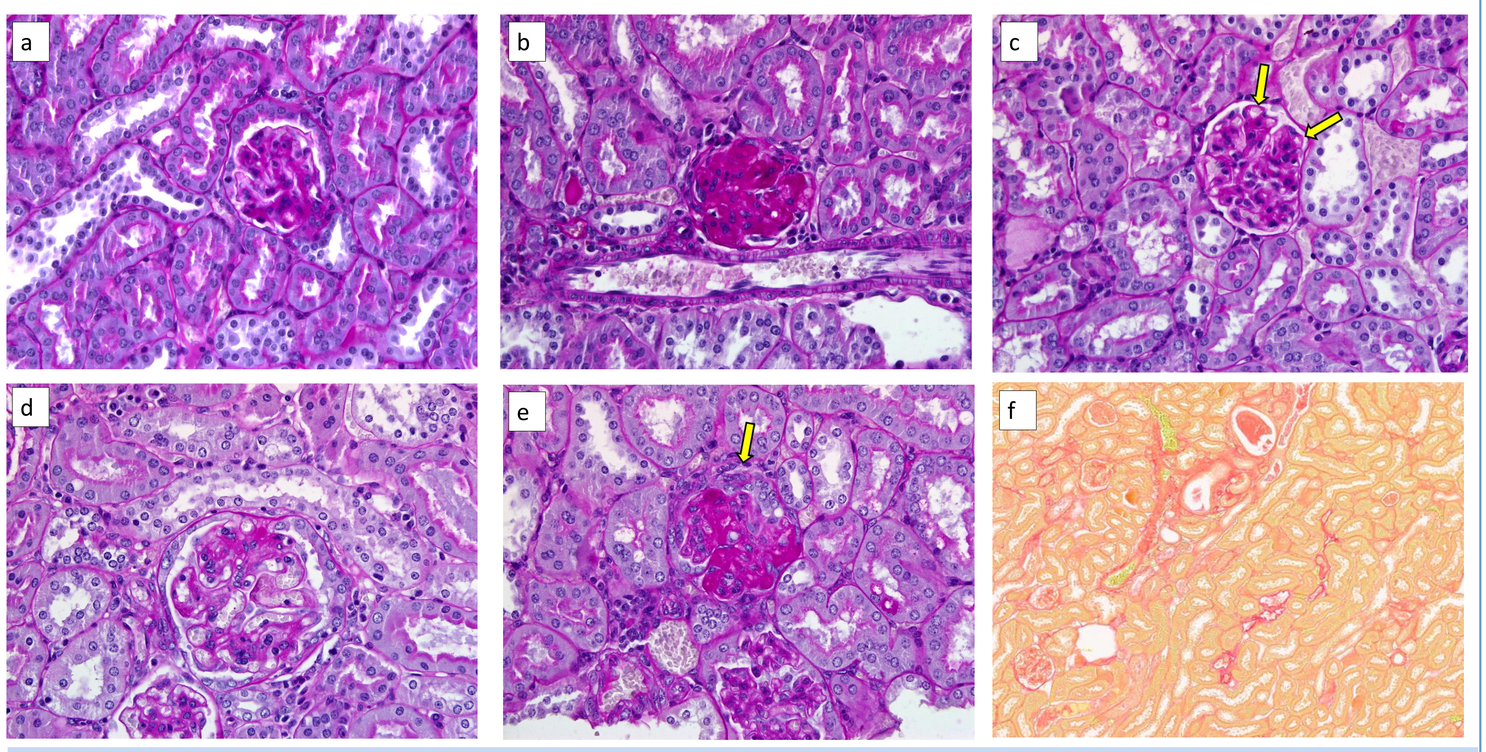
Validation experiment
Goal: Verify efficacy of known and experimental compounds

Key features of DN present in mouse model

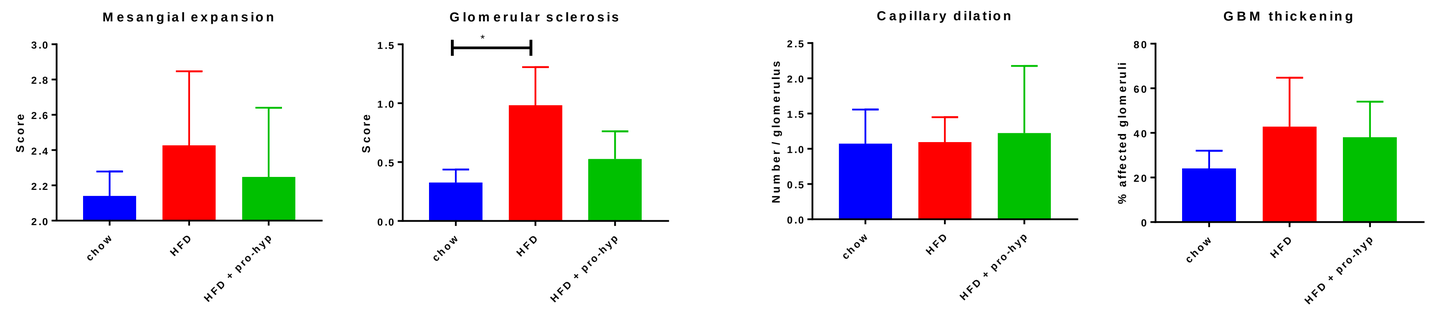


Combining UNX + HFD or HFD + a prohypertensive resulted in development of hyperlipidemia (a), hyperglycemia (b+c) and hypertension (d). A reduction of GFR is observed in the HFD+ prohypertensive group (e). Data are means ± SD.

Morphological changes of moderate DN



Morphological changes include mesangium expansion (a), glomerulosclerosis (b), GBM thickening (c), microaneurismata (d), arterial hyalinosis (e) and tubulo-interstitial fibrosis (f).



Conclusions

- We developed a mouse model which features three key components of DN in patients.
- The models shows features of advanced disease as shown by decreased GFR.
- Pathological changes include glomerulosclerosis and tubulo-interstitial fibrosis.
- Next steps will include a time-course study and verification of pharmacological interventions on disease development and progression.

› Arianne.vankoppen@tno.nl | +31 888 666 038 | www.tno.nl