Metabolic, biochemical, and histological effects of semaglutide in the ReninAAV UNx db/db mouse model of hypertension-accelerated diabetic kidney disease

Authors
Mette V. Østergaard, Michael Christensen, Casper Gravesen Salinas, Thomas Secher, Ida Rune, Henrik H. Hansen, Louise S. Dalbøge, Lisbeth N. Fink

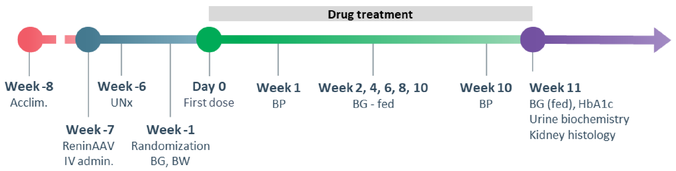
Gubra, Hørsholm Kongevej 11B, Hørsholm, Denmark

Corresponding author
Mette V. Østergaard - mvo@gubra.dk

BACKGROUND & AIM

Obesity, hyperglycaemia, and hypertension are critical risk factors for the onset and progression of diabetic kidney disease (DKD). Emerging evidence suggests that sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor (GLP-1R) agonists improve cardiovascular and renal outcomes in type 2 diabetes patients. The present study aimed to evaluate the therapeutic efficacy of the GLP-1R agonist semaglutide as monotherapy and as combination therapy with an ACE inhibitor, lisinopril, in the ReninAAV UNx db/db mouse model of hypertension-accelerated DKD.

1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	ReninAAV UNx db/db	Female	15	**Vehicle**	SC	QD	5 ml/kg	-
2	ReninAAV UNx db/db	Female	15	**Semaglutide**	SC	QD	5 ml/kg	**30 nmol/kg**
3	ReninAAV UNx db/db	Female	14	**Semaglutide + Lisinopril**	SC + PO	QD	5 ml/kg	**30 nmol/kg + 30 mg/kg**

Figure 1. Study outline, groups and treatments. BG: blood glucose, fed; BP: blood pressure measured by tail cuff; BW: body weight; IV: intravenous; QD: once daily; PO: peroral; ReninAAV: renin-encoding adeno-associated virus; SC: subcutaneous; UNx: uninephrectomy.

2 Improvement in metabolic and biochemical parameters

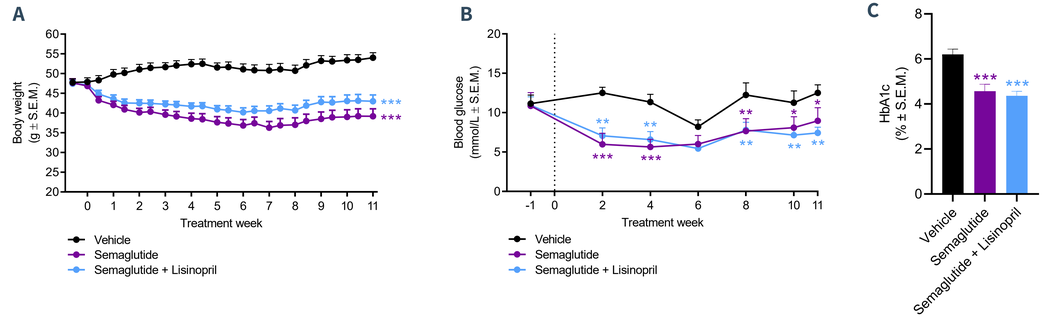


Figure 2. Semaglutide reduces body weight and biochemical parameters in ReninAAV UNx db/db mice. **(A)** Body weight (first dose day 0). **(B)** Fed blood glucose measured bi-weekly and at termination. **(C)** Terminal HbA1c. *p<0.05, **p<0.01, ***p<0.001 compared to vehicle dosed ReninAAV UNx db/db mice.

3 Improvement in hypertension

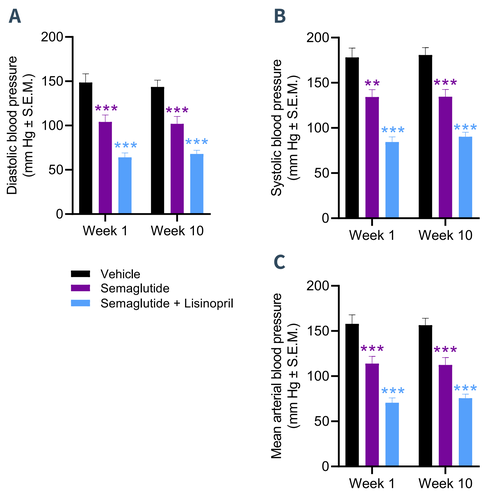


Figure 3. Semaglutide improves blood pressure in ReninAAV UNx db/db mice. Blood pressure was measured in conscious mice by tail cuff after 1 and 10 weeks of drug treatment. **(A)** Diastolic blood pressure. **(B)** Systolic blood pressure. **(C)** Mean arterial pressure.**p<0.01, p<0.001 compared to vehicle-dosed ReninAAV UNx db/db mice.

4 Reduced albuminuria and KIM-1 excretion

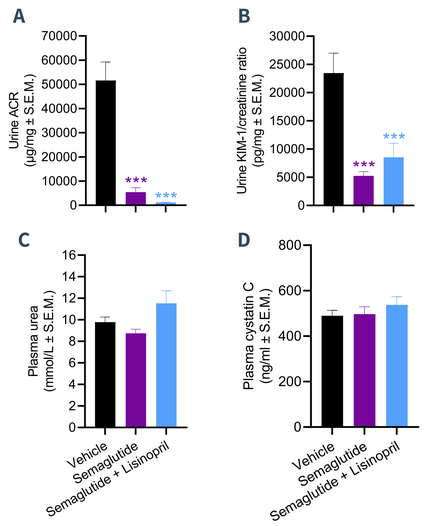


Figure 4. Semaglutide improves urine, but not plasma, markers of kidney injury in ReninAAV UNx db/db mice. Biochemical assessment of urine and plasma markers of kidney injury and function after 11 weeks of drug treatment. **(A)** Albumin-to-creatinine ratio in spot urine samples. **(B)** KIM-1-to-creatinine ratio in spot urine samples. **(C)** Terminal plasma urea. **(D)** Terminal plasma cystatin C. ***p<0.001 compared to vehicle-dosed ReninAAV UNx db/db mice.

5 Improvement of glomerulosclerosis: AI-assisted histopathological scoring

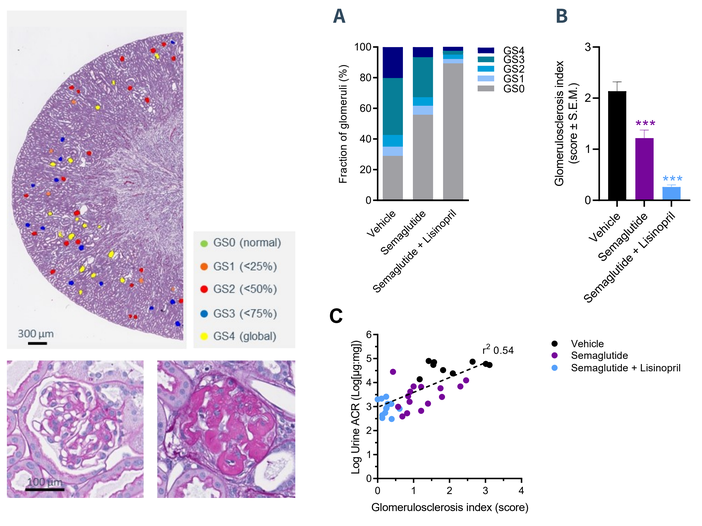


Figure 5. Semaglutide alone and in combination with lisinopril improves glomerulosclerosis in ReninAAV UNx db/db mice. Glomerulosclerosis was assessed in Periodic acid-Schiff (PAS)-stained kidney sections by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. Left panel shows a representative image from a vehicle-treated ReninAAV UNx db/db mouse kidney with visualization of scoring-based color code of individual glomeruli. Bottom panel shows glomeruli with glomerulosclerosis score (GS) 0 and 4, respectively. **(A)** Glomerulosclerosis score distribution. **(B)** Glomerulosclerosis index. ***p<0.001 compared to vehicle-dosed ReninAAV UNx db/db mice. **(C)** Correlation of glomerulosclerosis index and albuminuria.

CONCLUSION

- Semaglutide alone and in combination with lisinopril reduces body weight, blood glucose, and HbA1c.
- Blood pressure lowering effects of semaglutide are augmented by lisinopril.
- Semaglutide alone and in combination with lisinopril reduces albuminuria and KIM-1 excretion.
- Semaglutide alone and in combination with lisinopril promotes substantial improvements in glomerulosclerosis.
- These findings support nephroprotective effects of semaglutide in DKD, and highlights clinical translatability and applicability of the ReninAAV UNx db/db mouse model in preclinical drug development.

www.gubra.dk