Nephroprotective effects of semaglutide in a mouse model of hypertension-accelerated diabetic kidney disease

Authors
Stine T. Bak[1], Louise S. Dalbøge[1], Michael Christensen[1], Thomas Secher[1], Martin R. Madsen[1], Henrik H. Hansen[1], Ida Rune[1], Lisbeth N. Fink[1], Mette V. Østergaard[1] .

[1] Gubra, Hørsholm Kongevej 11B, Hørsholm, Denmark

Corresponding author
Michael Christensen - mch@gubra.dk

BACKGROUND & AIM

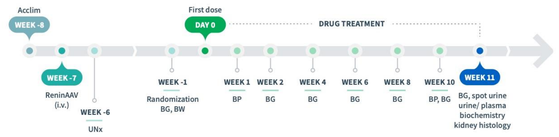
Obesity, hyperglycemia and hypertension are critical risk factors for development of diabetic kidney disease (DKD). Emerging evidence suggests that glucagon-like peptide-1 receptor (GLP-1R) agonists improve cardiovascular and renal outcomes in type 2 diabetes patients.
Here, we characterized the effect of long-acting GLP-1R agonist semaglutide monotherapy and in combination with an ACE inhibitor in a mouse model of hypertension-accelerated advanced DKD, facilitated by adeno-associated virus-mediated renin overexpression (ReninAAV) in uninephrectomized (UNx) female diabetic db/db mice.

METHODS

Female db/db mice received an intravenous Renin-encoding AAV injection one week prior to UNx. Six weeks post-UNx, db/db UNx-ReninAAV mice were randomized and stratified to treatment groups based on body weight and fed blood glucose levels. db/db UNx-ReninAAV mice received (q.d.) vehicle, semaglutide (30 nmol/kg, s.c.), or semaglutide (30 nmol/kg, s.c.) + lisinopril (30 mg/kg, p.o.) for 11 weeks. Endpoints included blood pressure, plasma/urine biochemistry and kidney histopathology.

www.gubra.dk

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

2 Improvements in metabolic parameters

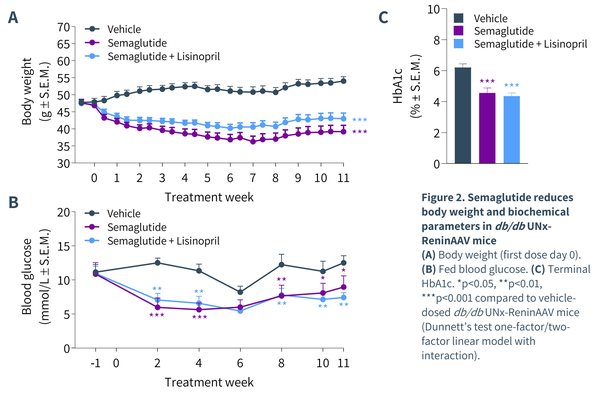


Figure 2. Semaglutide reduces body weight and biochemical parameters in *db/db* UNx-ReninAAV mice
(A) Body weight (first dose day 0). **(B)** Fed blood glucose. **(C)** Terminal HbA1c. *p<0.05, **p<0.01, ***p<0.001 compared to vehicle-dosed *db/db* UNx-ReninAAV mice (Dunnett's test one-factor/two-factor linear model with interaction).

3 Reduces hypertension

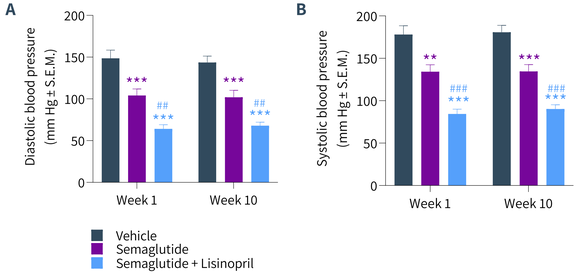


Figure 3: Semaglutide improves hypertension in *db/db* UNx-ReninAAV mice
(A) Diastolic arterial blood pressure. **(B)** Systolic arterial blood pressure. ***p<0.001 vs vehicle-dosed *db/db* UNx-ReninAAV mice. ##p<0.01, ###p<0.001 vs. semaglutide (Dunnett's test two-factor linear model with interaction).

4 Reduces albuminuria and KIM-1 excretion

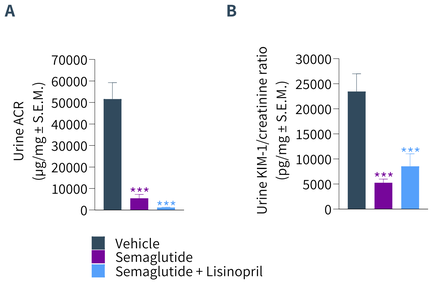


Figure 4. Semaglutide improves severe albuminurea and urinary KIM-1 excretion in *db/db* UNx-ReninAAV mice (A) Albumin-to-creatinine ratio. **(B)** KIM-1-to-creatinine ratio. Spot urine samples. ***p<0.001 compared to vehicle-dosed *db/db* UNx-ReninAAV mice (Dunnett's test one-factor linear model with interaction).

5 Semaglutide alone and in combination with lisinopril reduces glomerulosclerosis

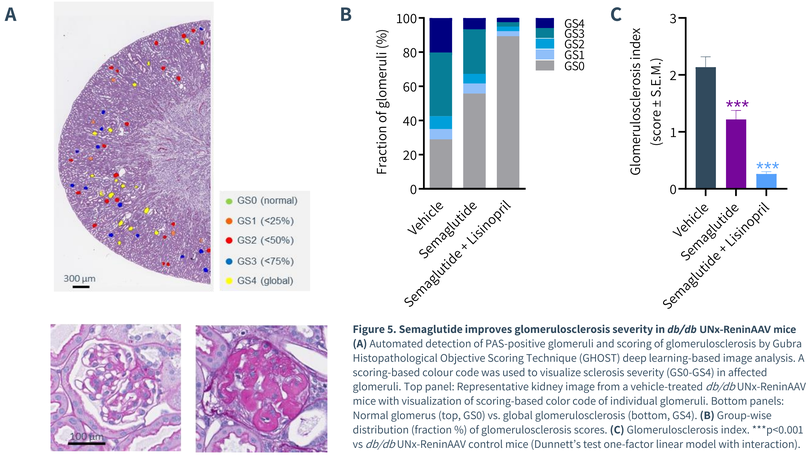


Figure 5. Semaglutide improves glomerulosclerosis severity in *db/db* UNx-ReninAAV mice
(A) Automated detection of PAS-positive glomeruli and scoring of glomerulosclerosis by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. A scoring-based colour code was used to visualize sclerosis severity (GS0-GS4) in affected glomeruli. Top panel: Representative kidney image from a vehicle-treated *db/db* UNx-ReninAAV mice with visualization of scoring-based color code of individual glomeruli. Bottom panels: Normal glomerus (top, GS0) vs. global glomerulosclerosis (bottom, GS4). **(B)** Group-wise distribution (fraction %) of glomerulosclerosis scores. **(C)** Glomerulosclerosis index. ***p<0.001 vs *db/db* UNx-ReninAAV control mice (Dunnett's test one-factor linear model with interaction).

CONCLUSION

Semaglutide alone and in combination with lisinopril:

+ Reduces body weight, blood glucose and HbA1c
+ Improves hypertension
+ Reduces albuminuria and urinary KIM-1 excretion
+ Promotes substantial improvements in glomerulosclerosis

These findings support nephroprotective effects of semaglutide in DKD, and highlights the applicability of the db/db UNx-ReninAAV mouse model in preclinical drug development.

Scan the QR code to see the paper:
Dalbøge, L.S., Christensen, M. *et al.* Nephroprotective Effects of Semaglutide as Mono- and Combination Treatment with Lisinopril in a Mouse Model of Hypertension-Accelerated Diabetic Kidney Disease. Biomedicines 2022, 10: 1661.