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

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Background & Aim

Obesity, hyperglycemia and hypertension are critical risk factors for the development of diabetic cardiovascular disease (CVD) and diabetic kidney disease (DKD) .

Emerging evidence suggests that glucagon-like peptide-1 receptor agonists (GLP-1RAs) improve cardiovascular and renal outcomes in type 2 diabetic patients.

Here, we characterized the cardiovascular effects of semaglutide, a long-acting GLP-1RA, 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

See study outline. Female diabetic *db/db* mice (12 weeks old) received a single IV dose of renin-encoding AAV by study week -5 and underwent unilateral nephrectomy at study week -4. *db/db* UNx-ReninAAV mice were randomized into treatment groups based on body weight, urinary albumin-to-creatinine ratio (uACR) and fed blood glucose (BG) levels. *db/db* UNx-ReninAAV mice were administered (SC) vehicle or semaglutide (20 nmol/kg) once daily and terminated after 12 weeks of treatment. Vehicle-dosed *db*+ mice served as normal controls. Endpoints included heart weight, uACR, whole-heart 3D imaging (Fast Green stain, Masson's trichrome collagen labelling dye) and kidney histopathology.

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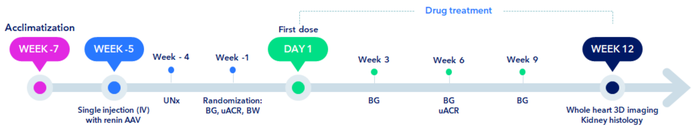
1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	Db/+	Female	9	**Vehicle**	SC	QD	5 ml/kg	-
2	ReninAAV UNx db/db	Female	17	**Vehicle**	SC	QD	5 ml/kg	-
3	ReninAAV UNx db/db	Female	13	**Semaglutide**	SC	QD	5 ml/kg	**20 nmol/kg**

2 Semaglutide improves metabolic endpoints

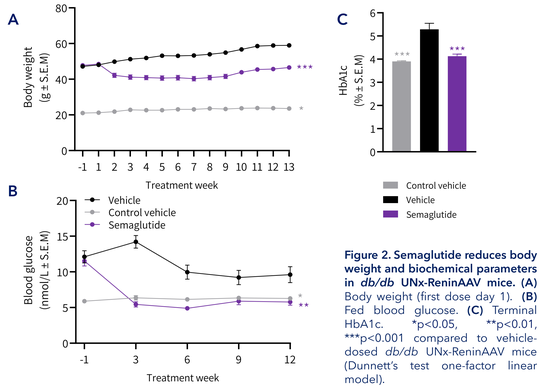


Figure 2. Semaglutide reduces body weight and biochemical parameters in *db/db* UNx-ReninAAV mice. (A) Body weight (first dose day 1). **(B)** Fed blood glucose. **(C)** Terminal HbA1c. *p<0.05, **p<0.01, ***p<0.001 compared to vehicle-dosed *db/db* UNx-ReninAAV mice (Dunnett's test one-factor linear model).

3 Semaglutide reduces whole-heart fibrosis

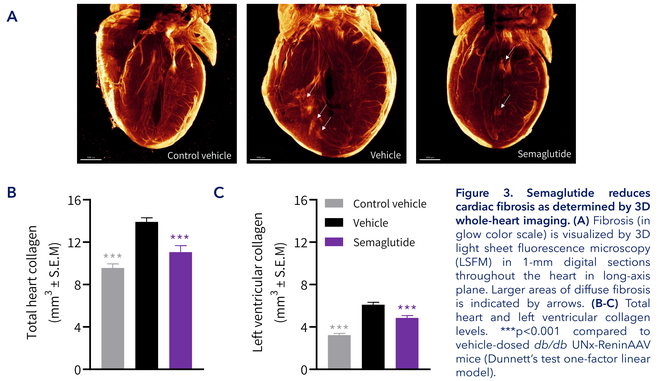


Figure 3. Semaglutide reduces cardiac fibrosis as determined by 3D whole-heart imaging. (A) Fibrosis (in glow color scale) is visualized by 3D light sheet fluorescence microscopy (LSFM) in 1-mm digital sections throughout the heart in long-axis plane. Larger areas of diffuse fibrosis is indicated by arrows. **(B-C)** Total heart and left ventricular collagen levels. ***p<0.001 compared to vehicle-dosed *db/db* UNx-ReninAAV mice (Dunnett's test one-factor linear model).

4 Semaglutide reduce cardiac hypertrophy

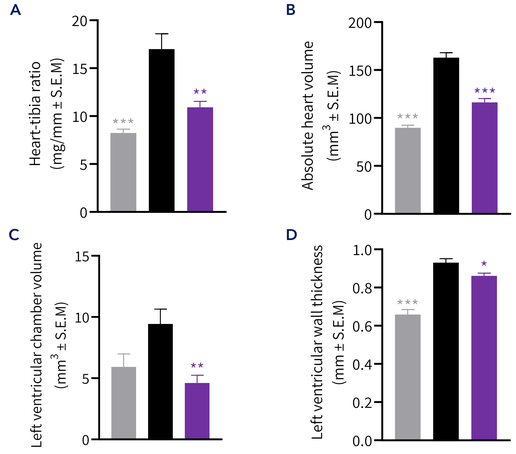


Figure 4. Semaglutide improves cardiac hypertrophy. (A) Heart-tibia ratio. **(B)** Absolute heart volume. **(C)** Left ventricular chamber volume. **(D)** Left ventricular wall thickness. *p<0.05, **p<0.01, ***p<0.001 compared to vehicle-dosed *db/db* UNx-ReninAAV mice (Dunnett's test one-factor linear model).

5 Semaglutide reduces kidney injury

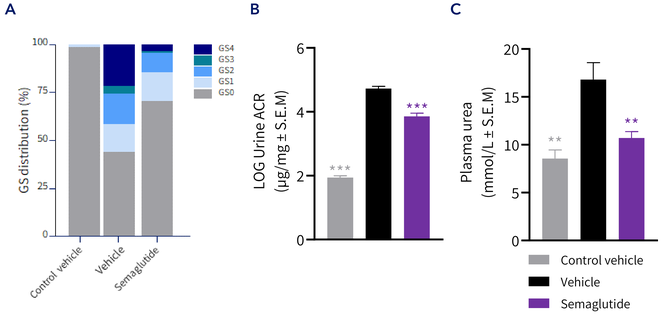


Figure 5. Semaglutide improves glomerulosclerosis severity and plasma urea levels in *db/db* UNx-ReninAAV mice. (A) Group-wise distribution (fraction %) of glomerulosclerosis scores. Automated detection of PAS-positive glomeruli and scoring of glomerulosclerosis by deep learning-based image analysis (Gubra Histopathological Objective Scoring Technique, GHOST). A scoring-based color code was used to visualize sclerosis severity (GS0-GS4) in affected glomeruli. **(B)** Albumin-to-creatinine ratio measured in spot urine. **(C)** Plasma urea measured in terminal plasma. **p<0.01, ***p<0.001 compared to vehicle-dosed db/db UNx-ReninAAV mice (Dunnett's test one-factor linear model).

Conclusion

- *db/db* ReninAAV UNx mice present with cardiac fibrosis, concentric cardiac hypertrophy as well as glomerulosclerosis and albuminuria
- Semaglutide reduces body weight, blood glucose and HbA1c
- Semaglutide reduces cardiac fibrosis
- Semaglutide improves cardiac hypertrophy and left ventricular dilation
- Semaglutide improves glomerulosclerosis

These findings support cardiorenal protective effects of semaglutide in CVD and DKD and highlights the applicability of the *db/db* UNx-ReninAAV mouse model in preclinical drug development.

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