Nephroprotective effects of dapagliflozin in the adenine-diet induced mouse model of chronic kidney disease

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Background & Aim

Translational models are essential to identify improved treatment options for chronic kidney disease (CKD) patients. However, most preclinical CKD models do not demonstrate reduced glomerular filtration rate (GFR) or improvement by standard of care (SoC).

The present study aimed to evaluate SoC using a sodium-glucose cotransporter type 2 inhibitor (SGLT2i) in the adenine-induced mouse model of CKD.

Methods

See study outline. Male C57BL/6JRj mice (11 weeks old) were randomised into study groups based on body weight. From day 1, control mice received control diet (S9352-E064, Ssniff, Germany), and adenine mice received 0.2% adenine (S9352-E060, Ssniff, Germany). Adenine diet-induced (ADI) mice were either treated with vehicle or Dapagliflozin (10 mg/kg, PO, BID). At week 3, urine albumin-to-creatinine ratio (uACR) and cystatin C was measured. GFR was measured and calculated based on $T_{1/2}$ of FITC-sinistrin clearance. Terminal plasma was collected for evaluation of urea, creatinine, cystatin C levels. The left kidney was weighed and processed for histomorphometric assessment of fibrosis (Col3a1), tubular injury (KIM-1) and macrophage infiltration (F4/80).

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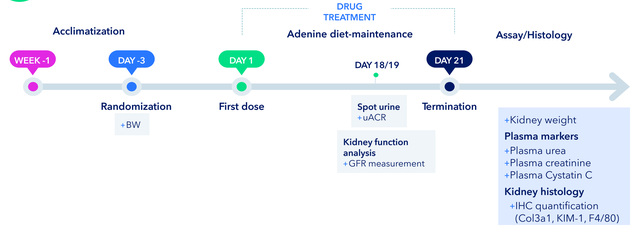
1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	Control diet	Male	8	**Vehicle**	PO	Twice daily	5 ml/kg	-
2	Adenine diet (ADI)	Male	8	**Vehicle**	PO	Twice daily	5 ml/kg	-
3	Adenine diet (ADI)	Male	10	**Dapagliflozin**	PO	Twice daily	5 ml/kg	**10 mg/kg**

2 Dapagliflozin reverses progressive weight loss

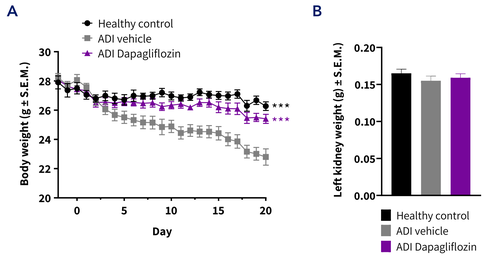


Figure 2. Dapagliflozin reverses progressive weight loss in ADI mice. (A) Body weight. **(B)** Left kidney weight. ***p<0.001 compared to ADI vehicle mice (Dunnett's test one-factor linear model).

3 Dapagliflozin improves kidney function

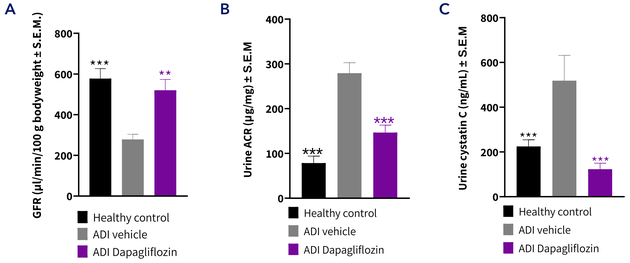
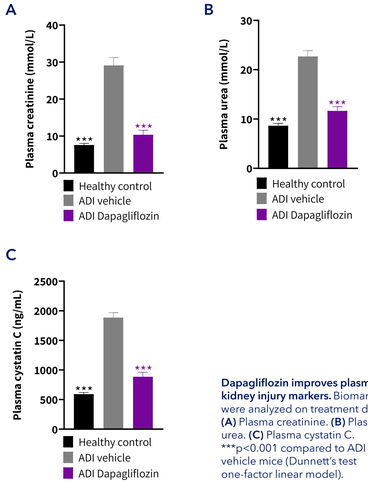


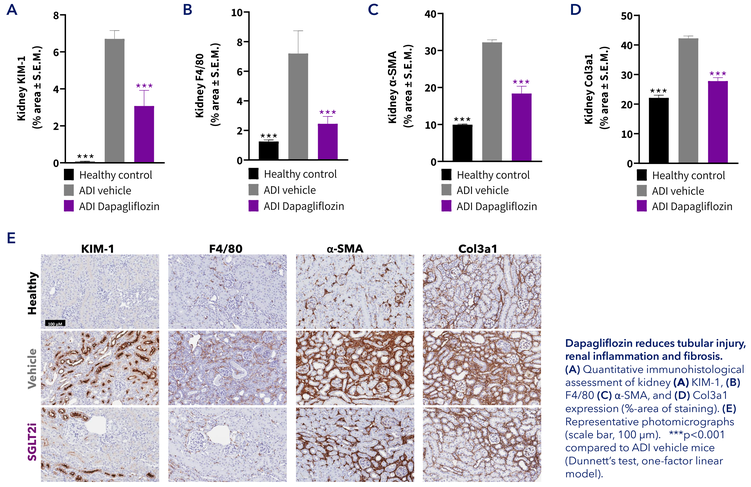
Figure 3. Dapagliflozin improves GFR and uACR. (A) GFR at week 3. **(B)** Urine ACR at week 3. **(C)** Urine cystatin C at week 3. **p<0.01, ***p<0.001 compared to ADI vehicle mice (Dunnett's test one-factor linear model).

4 Dapagliflozin improves markers of renal function



Dapagliflozin improves plasma kidney injury markers. Biomarkers were analyzed on treatment day 21. **(A)** Plasma creatinine. **(B)** Plasma urea. **(C)** Plasma cystatin C. ***p<0.001 compared to ADI vehicle mice (Dunnett's test one-factor linear model).

5 Dapagliflozin reduces histological markers of kidney injury



Dapagliflozin reduces tubular injury, renal inflammation and fibrosis. **(A)** Quantitative immunohistological assessment of kidney **(A)** KIM-1, **(B)** F4/80 **(C)** α-SMA, and **(D)** Col3a1 expression (%-area of staining). **(E)** Representative photomicrographs (scale bar, 100 µm). ***p<0.001 compared to ADI vehicle mice (Dunnett's test, one-factor linear model).

Conclusion

The present study in ADI mice establishes that dapagliflozin

+ Improves GFR and albuminuria
+ Reduces plasma creatinine and urea
+ Reduces tubular injury
+ Reduces renal inflammation and fibrosis

These findings support nephroprotective effects of dapagliflozin in CKD and highlights the applicability of the ADI mouse model in preclinical drug development.

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