Adenine-induced Mouse Model of CKD rapidly develops declined Kidney Function, Renal Fibrosis, Muscle Wasting and Anemia

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Background & Aim

Translational models are essential to identify improved treatment options for CKD patients. However, most preclinical CKD models do not demonstrate reduced glomerular filtration rate (GFR).

The present study aimed to characterize the adenine diet-induced (ADI) mouse model of CKD for clinical translatability.

Methods

Male C57BL/6Rj mice (11 weeks) were randomized into 5 groups (n=8-10). Group 1 received a control diet from day -2 and were treated with Vehicle for 5 weeks. Group 2 to 5 received the control diet on day -2 and a CKD-inducing diet containing 0.2% adenine from day 1. All groups received vehicle administration (p.o.) once daily starting from day 1 until termination.

Urine creatinine/albumin and GFR was evaluated at week 3 and 5. Blood was collected for measurements of haemoglobin, and gastrocnemius muscle and kidney tissue was weighted, and kidneys were collected for RNA sequencing and quantitative histological evaluation of markers of macrophage infiltration (F4/80) and fibrosis (Col1a1).

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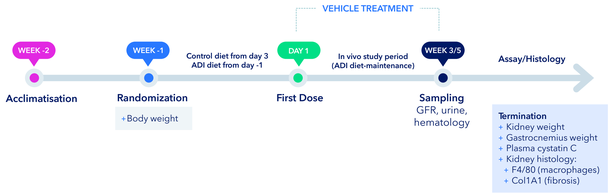
1 Study outline



Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume
1	Control diet	Male	10	**Vehicle**	PO	Once daily	5 ml/kg
2	Adenine diet (ADI)	Male	10	**Vehicle, 3 weeks**	PO	Once daily	5 ml/kg
3	Adenine diet (ADI)	Male	10	**Vehicle, 5 weeks**	PO	Once daily	5 ml/kg

2 Body weight and kidney weight

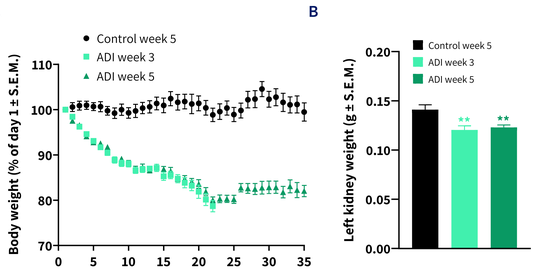


Figure 2. Body weight and kidney weight. **(A)** Body weight (% of day 1). **(B)** Kidney weight at termination. **P<0.01 vs. control mice (Dunnett's test one-factor linear model).

3 ADI-CKD mice develop decline in kidney function

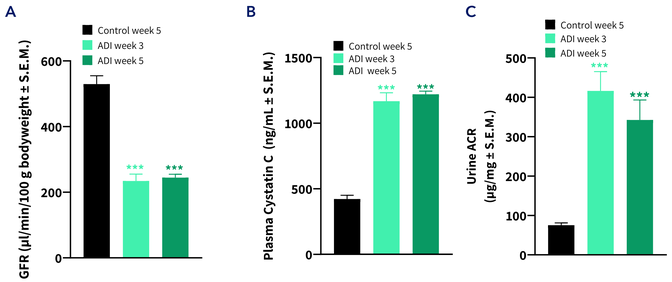


Figure 3. ADI-CKD mice develop decline in kidney function **(A)** Glomerular filtration rate (GFR) **(B)** Plasma cystatin C. **(C)** Urine albumin-to-creatinine ratio (ACR). ***P<0.001 vs. control mice (Dunnett's test one-factor linear model).

4 ADI-CKD mice develop muscle wasting and anemia

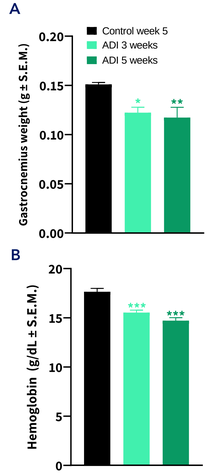


Figure 4. ADI-CKD mice develop muscle wasting and anemia. **(A)** Gastrocnemius weight. **(B)** Hemoglobin. *P<0.05, **P<0.01, ***P<0.001, compared to control mice (Dunnett's test one-factor linear model).

5 ADI-CKD mice develop renal inflammation and fibrosis

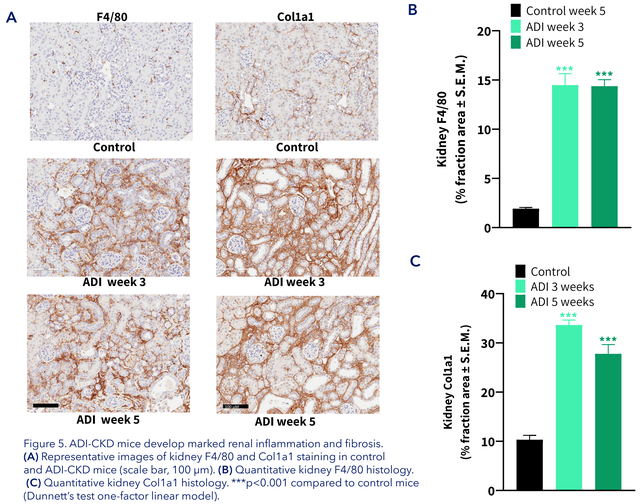


Figure 5. ADI-CKD mice develop marked renal inflammation and fibrosis. **(A)** Representative images of kidney F4/80 and Col1a1 staining in control and ADI-CKD mice (scale bar, 100 µm). **(B)** Quantitative kidney F4/80 histology. **(C)** Quantitative kidney Col1a1 histology. ***p<0.001 compared to control mice (Dunnett's test one-factor linear model).

6 Gene expression analysis

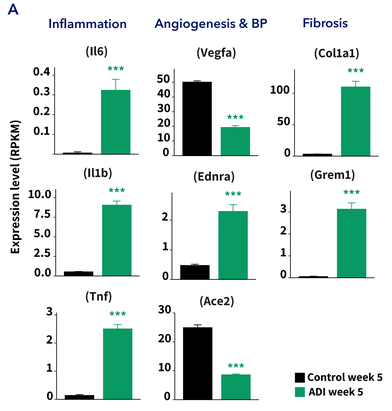


Figure 6. Gene expression analysis. **(A)** Expression levels of genes with differences in regulation directionality are shown as mean ± S.E.M RPKM values. ***p<0.001 compared to control week 5.

Conclusion

The ADI-CKD mouse demonstrates:

+ Reduced GFR
+ Muscle wasting and anaemia
+ Marked renal inflammation
+ Robust renal fibrosis

The ADI-CKD mouse is a translational model suitable for testing novel drug candidates for CKD.

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