Characterization of an adenine-diet induced (ADI) mouse model of chronic kidney disease with declining kidney function and renal fibrosis

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BACKGROUND & AIM

Chronic kidney disease (CKD) is characterized by a decreased kidney function diagnosed by reduced glomerular filtration rate (GFR) and elevated creatinine-to-albumin ratio (ACR). Translational models are essential to identify improved treatment options for CKD patients. However, most preclinical CKD models do not demonstrate reduced GFR.

Here, we characterize an adenine diet-induced (ADI) mouse model of CKD that enables translational studies of CKD. ADI mice show progressively declining kidney function, anaemia, infiltration of inflammatory cells and tubulointerstitial fibrosis within 3 weeks of adenine diet feeding.

METHODS

Male C57BL/6J mice (11 weeks old) were randomised into three groups based on body weight. All mice received a control diet (S9353-E064, Ssniff) from day -3. On day -1 mice were switched to 0.2 % adenine diet (S9352-E060, Ssniff) from day -1 and until termination (ADI-CKD mice) or remained on control diet. All groups received vehicle (PO) once daily starting on day 1. Urine creatinine/albumin and GFR was evaluated at week 3 and 5. Terminal endpoints included hematocrit and plasma cystatin C. Gastrocnemius muscle and kidney tissue was weighted and kidneys were processed for histological evaluation of markers of inflammation (F4/80) and fibrosis (Col1a1).

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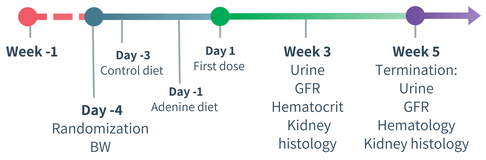
1 Study outline



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

2 Body weight and kidney weight at termination

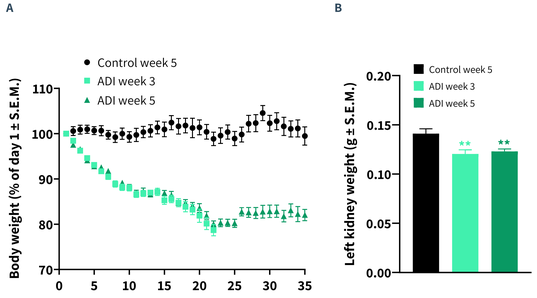


Figure 2. Body weight and kidney weight. (A) Body weight (% of day 1). **(B)** Kidney weight at termination. **P<0.01 vs. control mice (Dunnett's test one-factor linear model).

3 ADI-CKD mice show decline in kidney function

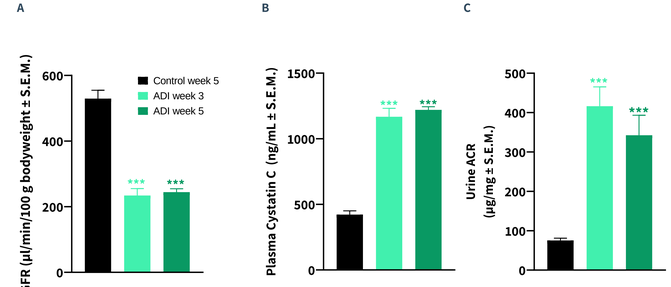


Figure 3. Declining kidney function in ADI-CKD mice. (A) Glomerular filtration rate (GFR) **(B)** Plasma cystatin C. **(C)** Urine albumin-to-creatinine ratio (ACR). ***P<0.001-vs. control mice (Dunnett's test one-factor linear model).

4 ADI-CKD mice develop muscle wasting and anemia

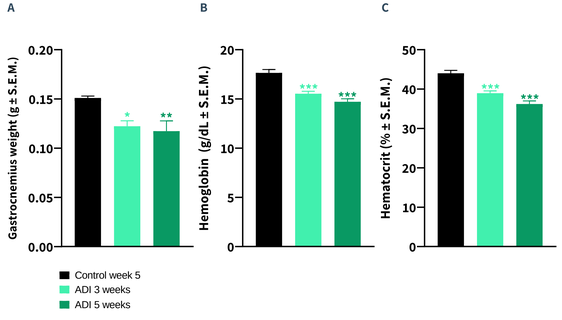


Figure 4. Muscle wasting and anemia.
(A) Gastrocnemius weight. **(B)** Hemoglobin **(C)** Hematocrit. *P<0.05, **P<0.01, ***P<0.001, compared to control mice (Dunnett's test one-factor linear model).

5 ADI-CKD mice show renal inflammation

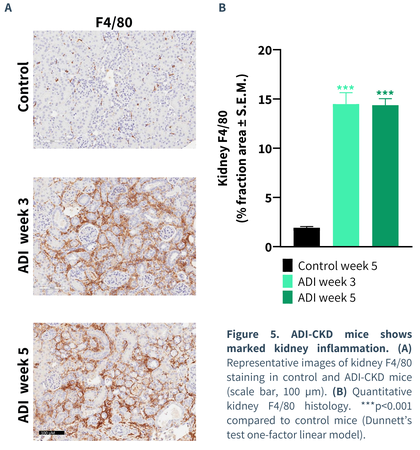


Figure 5. ADI-CKD mice shows marked kidney inflammation. (A) Representative images of kidney F4/80 staining in control and ADI-CKD mice (scale bar, 100 µm). **(B)** Quantitative kidney F4/80 histology. ***p<0.001 compared to control mice (Dunnett's test one-factor linear model).

6 ADI-CKD mice show robust kidney fibrosis

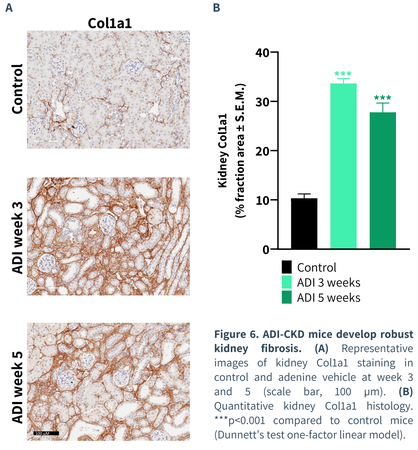


Figure 6. ADI-CKD mice develop robust kidney fibrosis. (A) Representative images of kidney Col1a1 staining in control and adenine vehicle at week 3 and 5 (scale bar, 100 µm). **(B)** Quantitative kidney Col1a1 histology. ***p<0.001 compared to control mice (Dunnett's test one-factor linear model).

CONCLUSION

The ADI-CKD mouse demonstrates:

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

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

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