The adenine-induced mouse model of CKD shows rapid development of impaired kidney function, anaemia, muscle wasting and renal fibrosis

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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), which is a hallmark of CKD.

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 (p.o.) once daily starting from day 1 until termination.

Urine albumin-to-creatinine ratio (uACR), plasma cystatin C (PCyC) and GFR was evaluated at week 3 and 5. Blood was collected for haemoglobin measurement, and gastrocnemius muscle and kidney tissue was weighted, and kidneys were collected for quantitative histological evaluation of markers of macrophage infiltration (F4/80) and fibrosis (Col1a1). In a parallel study, ADI mice (3 weeks on ADI diet) were switched to control diet for 2 weeks (diet reversal) to test for spontaneous regression of kidney biomarker and histological changes (PCyC, F4/80, Col1a1).

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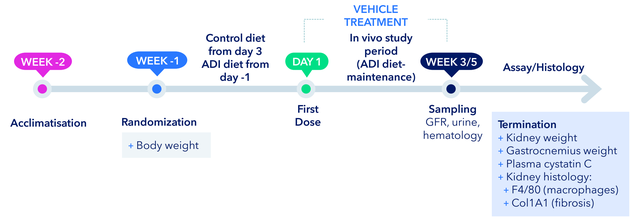
1 Study outline



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

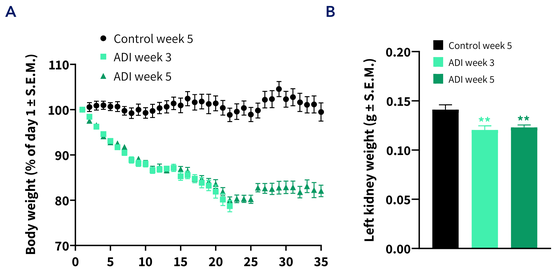


Figure 2. Body weight and kidney weight. (A) Body weight (% of day 1). **(B)** Kidney weight at termination. Data is shown as mean ± S.E.M. **P<0.01 vs. control mice (Dunnett's test one-factor linear model).

3 ADI-CKD mice demonstrate impaired kidney function

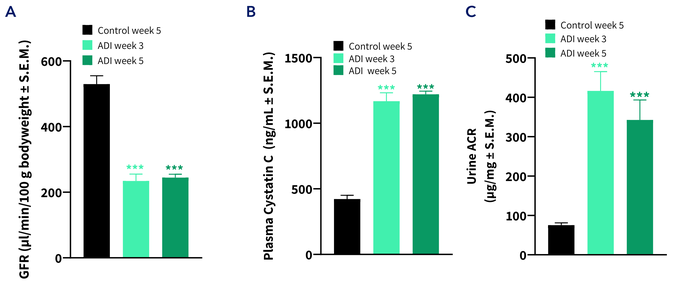


Figure 3. ADI-CKD mice develop decline in kidney function (A) Glomerular filtration rate (GFR) **(B)** Plasma cystatin C. **(C)** Urine albumin-to-creatinine ratio (ACR). Data is shown as mean ± S.E.M. ***P<0.001 vs. control mice (Dunnett's test one-factor linear model).

4 Muscle wasting and anemia

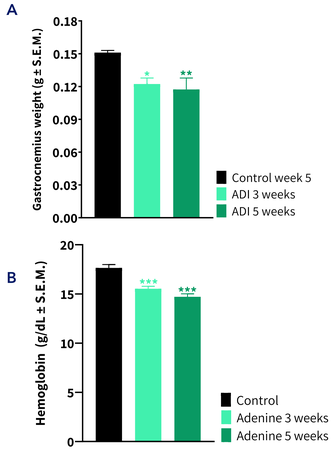


Figure 4. ADI-CKD mice develop muscle wasting and anemia. **(A)** Gastrocnemius weight. **(B)** Hemoglobin. *P<0.05, **P<0.01, ***P<0.001, compared to control mice (Dunnett's test one-factor linear model).

5 ADI-CKD mice show renal inflammation and fibrosis

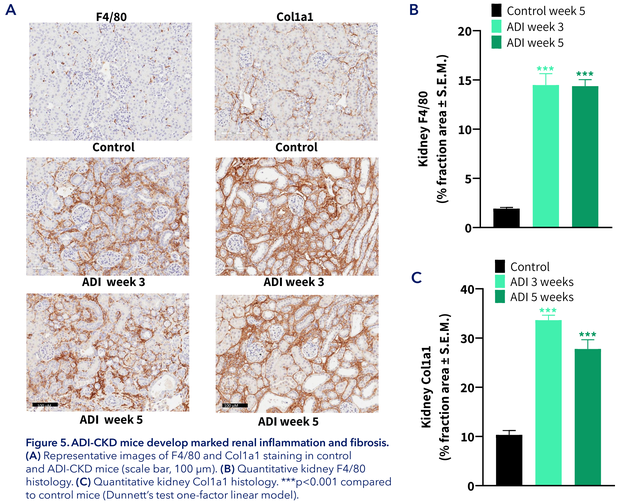


Figure 5. ADI-CKD mice develop marked renal inflammation and fibrosis. **(A)** Representative images of F4/80 and Col1a1 staining in control and ADI-CKD mice (scale bar, 100 µm). **(B)** Quantitative kidney F4/80 histology. **(C)** Quantitative kidney Col1a1 histology. ***p<0.001 compared to control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

6 Dietary reversal

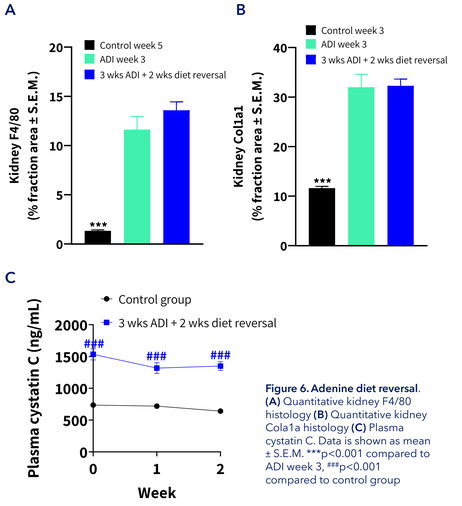


Figure 6. Adenine diet reversal. **(A)** Quantitative kidney F4/80 histology **(B)** Quantitative kidney Cola1a histology **(C)** Plasma cystatin C. Data is shown as mean ± S.E.M. ***p<0.001 compared to ADI week 3, ###p<0.001 compared to control group

Conclusion

The ADI-CKD mouse demonstrates:

+ Impaired GFR
+ Muscle wasting and anaemia
+ Persistent inflammation and fibrosis

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

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