Florida Chapter, American College of Surgeons 2021 Annual Meeting
Resident Paper Competition

Title

Partial Nephrectomy Versus Diet-Induced Nephropathy: Comparing Murine Models of Renal Dysfunction

Authors

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Background

Chronic kidney disease(CKD) affects approximately 15% of patients and is associated with significant morbidity. The complex pathobiology of CKD and its relationship to a variety of disease states is poorly understood. Moreover, a paucity of treatment strategies exist that target biologic impacts of CKD, highlighting the importance of developing valid animal models. Murine models classically utilize surgical renal volume reduction strategies(5/6th partial nephrectomy[PN]). Notably, adenine metabolites cause renal parenchymal injury and adenine dietary-induced(AD) CKD models are increasingly reported. AD models are an attractive alternative to PN due to ease of induction and obviation of surgical morbidity. However, to date, no comparative studies between PN and AD mice models have been performed. We hypothesize that AD and PN models produce comparable levels of renal dysfunction and pathological derangements, with a secondary AD survival benefit.

Methods

C57BL/6J mice(10-12 weeks old) were divided into four groups(equal male:female). 12 mice were fed an adenine-supplemented diet(AD), while 10 controls received casein-based chow. Surgical cohorts included 21 PN mice and 12 sham controls. PN included left upper and lower pole resection followed by right nephrectomy 1-week later. Kidney function was assessed with GFR and BUN before sacrifice at 6-weeks post-operatively. Muscle wasting, as a surrogate for CKD physiological impact, was measured by body weight, muscle mass, and myofiber area at time of sacrifice.

Results

Mean GFR was similar between AD and PN mice for both male(81.1μL/min, 160.0μL/min, p=0.53) and female(125.2μL/min, 107.0μL/min, p=0.98) animals. Compared to diet and surgical controls, similarly significant decreases in GFR were evident for both PN and AD groups($p<0.001$)(Fig.1). However, mean BUN values were significantly higher in PN cohorts($p<0.0001$). In contrast, only male AD mice had significantly higher BUN values relative to diet controls(male, p=0.02; female, p=0.20). Uremia severity varied across groups(male: AD 57.5mg/dL, PN 109.9mg/dL; $p<0.0001$)(female: 49.4mg/dL AD, 74.6mg/dL PN; p=0.0491)(Fig.2).

Male AD and PN mice had reduced body weight($p<0.0001$), muscle mass(AD $p<0.05$ each; PN $p<0.001$ each), and myofiber area($p<0.05$) compared to controls. The magnitude of muscle wasting was equivalent in AD and PN male mice. Notably, body weight loss and muscle wasting were absent in female mice(Fig.3,4). PN survival was 50% for males and 82% for females, while no deaths occurred in the other cohorts(Fig.5,6).

Conclusion

In male mice, AD nephropathy is comparable to PN with no difference in GFR reduction or degree of muscle wasting. However, PN mice have worse uremia compared to AD animals. Female AD mice have no difference in uremia or muscle wasting relative to controls, and likely this experiment was underpowered to detect the impact of minor perturbations in renal function in this cohort. Smaller female size compounds the lack of dissimilarity since muscle wasting differences were not observed in PN mice either. The similar renal dysfunction and improved mortality for male mice, combined with the known benefits of a non-invasive and simplified experimental protocol, make AD nephropathy an ideal murine CKD model.

Figures

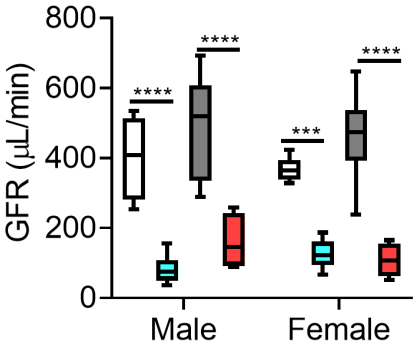

Figure 1: Glomerular Filtration Rate

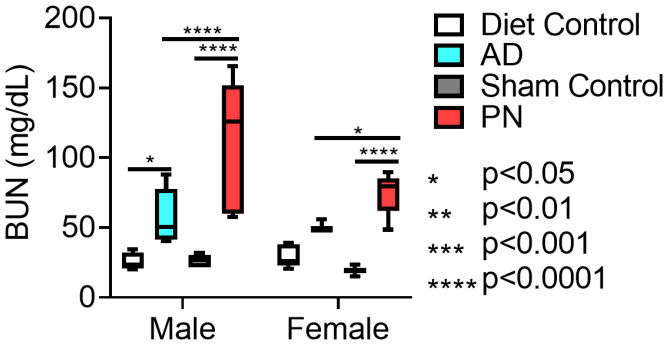

Figure 2: Blood Urea Nitrogen

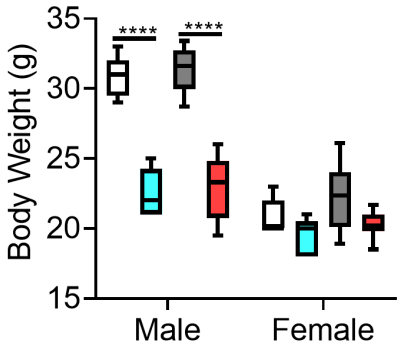

Figure 3: Body Weight

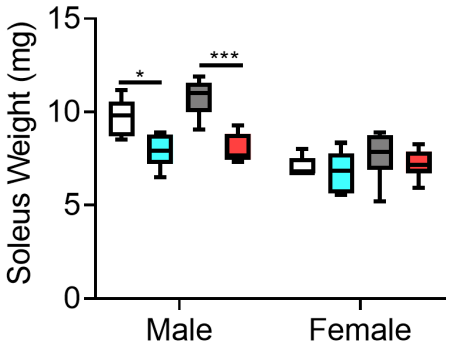

Figure 4: Muscle Mass, Soleus

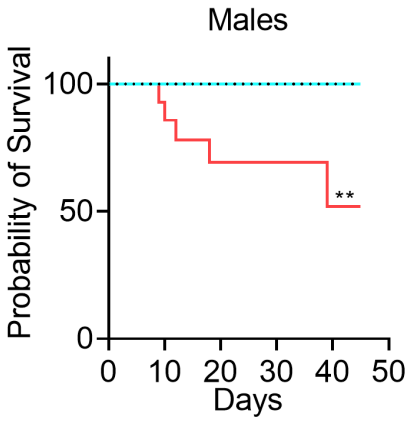

Figure 5: Male Survival Curve

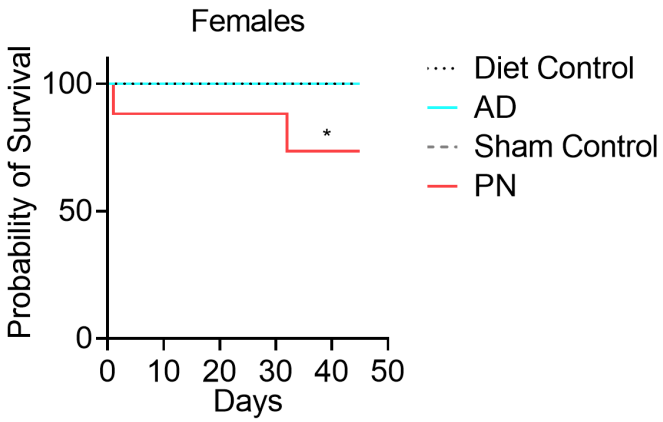

Figure 6: Female Survival Curve