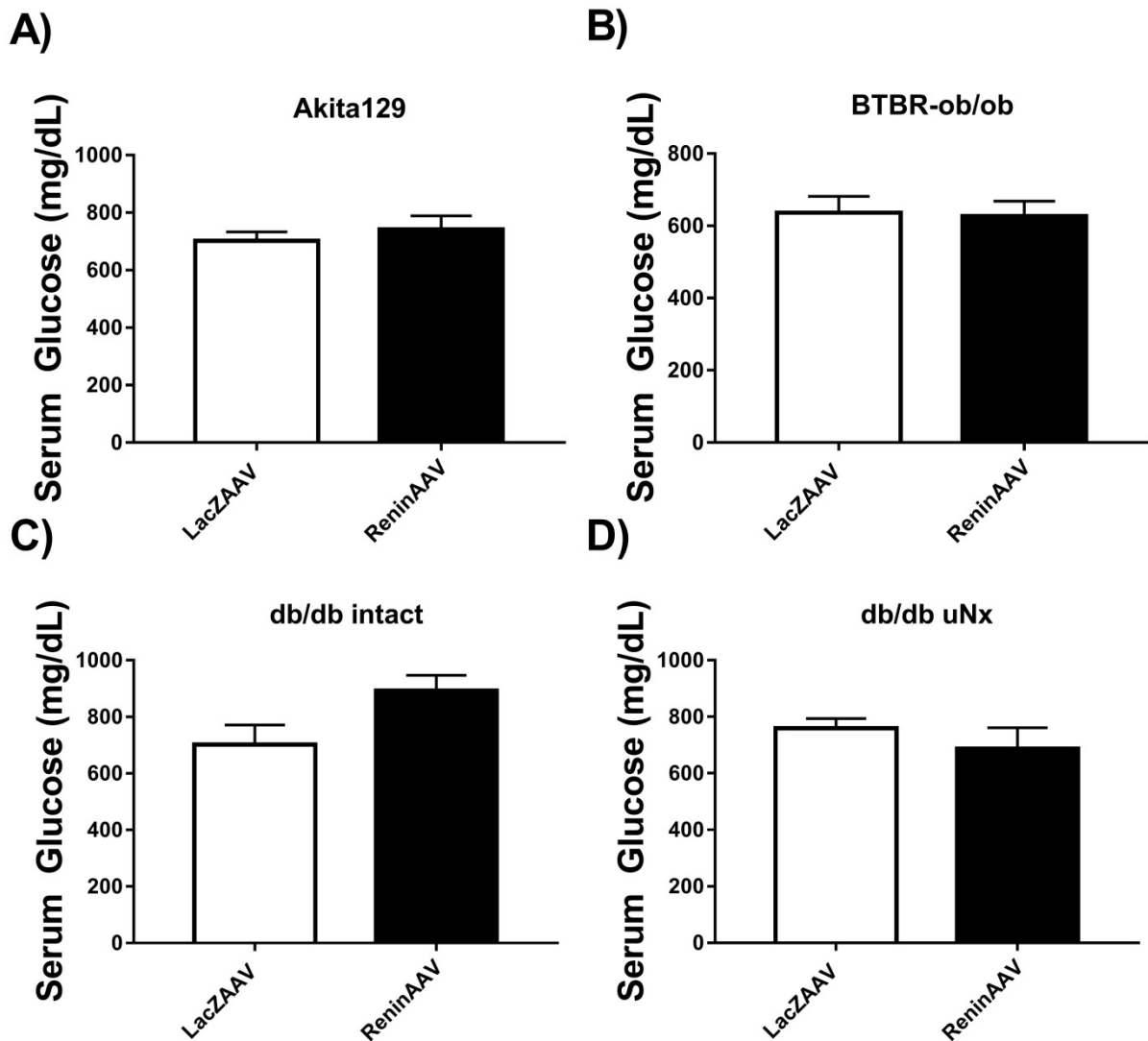


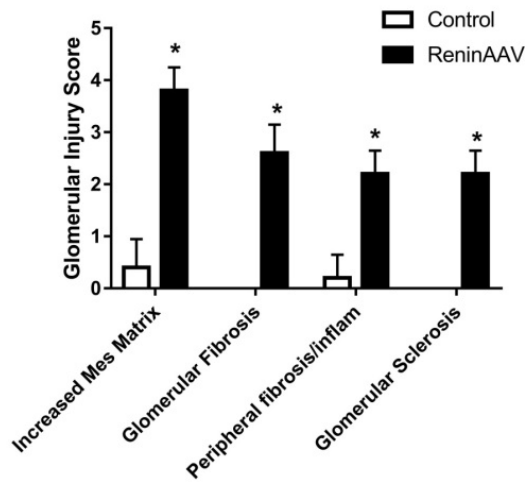
Supplementary Figure 1:



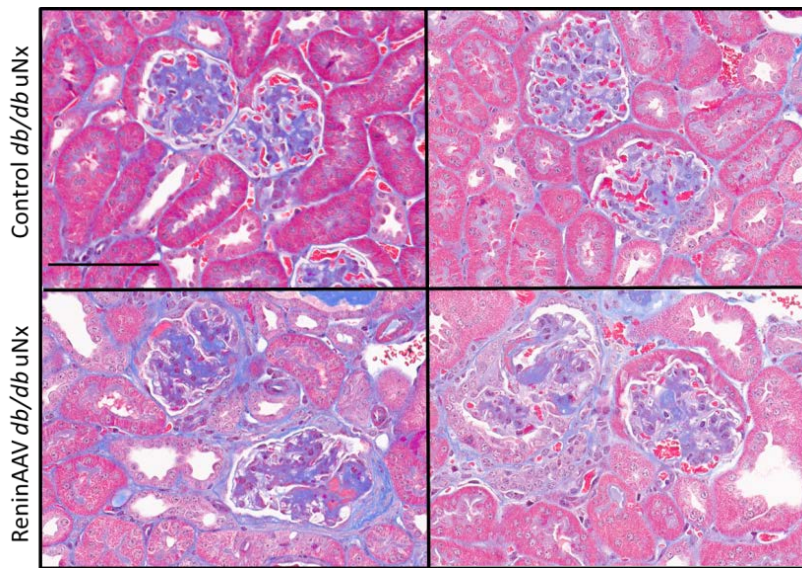
**Supplementary Figure 1:** ReninAAV effects on renal disease progression were independent of changes in serum glucose levels. Serum glucose was measured after 8-12 weeks of ReninAAV with no significant difference compared to LacZ controls in Akita/129 (A), BTBR-ob/ob (B), db/db intact (C) or db/db uNx (D) mice.

Supplementary Figure 2:

A)

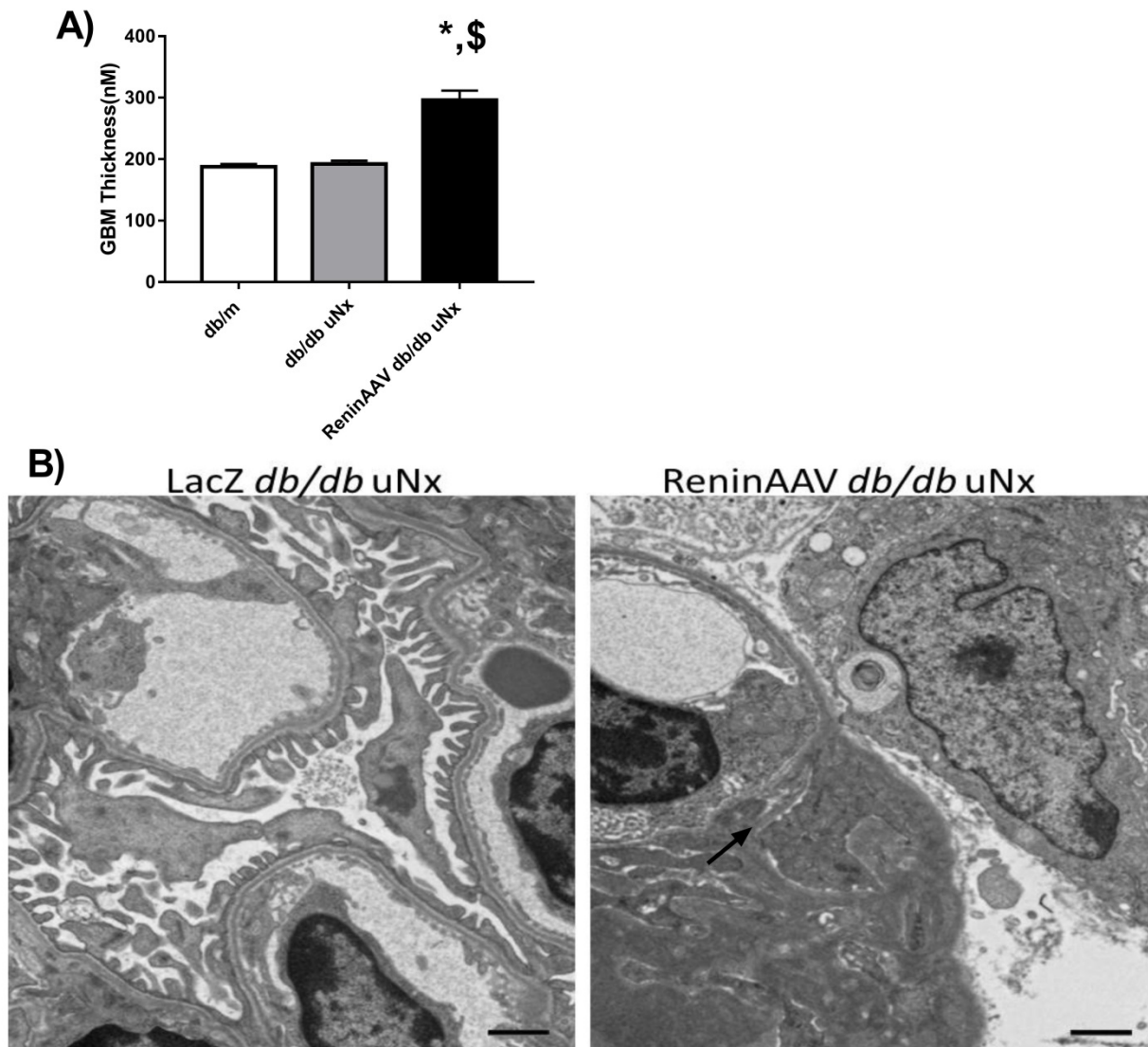


B)



**Supplementary Figure 2:** Pathological changes in the glomerulus of ReninAAV *db/db* uNx model. (A) Summary of quantitative assessment of histopathological changes observed in the glomerulus of the ReninAAV *db/db* uNx model as compared the control *db/db* uNx mice (\* $p < 0.05$ ). (B) Representative MTS images from ReninAAV *db/db* uNx mice compared to control *db/db* uNx mice (scale bar 100 $\mu$ M).

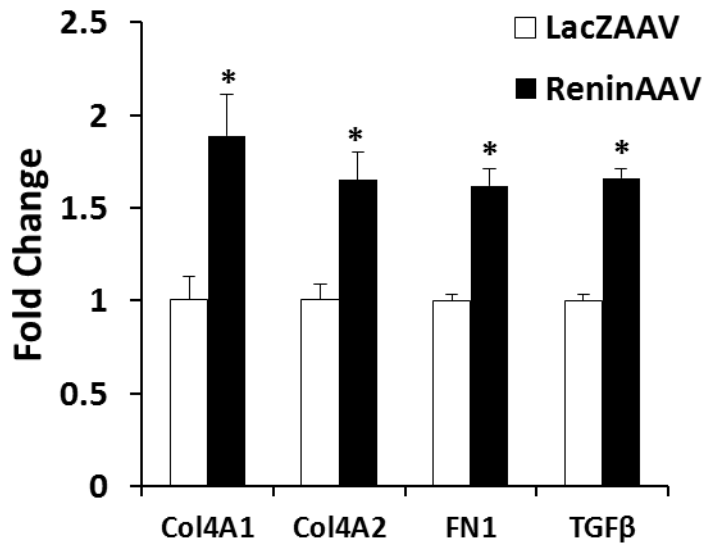
**Supplementary Figure 3:**



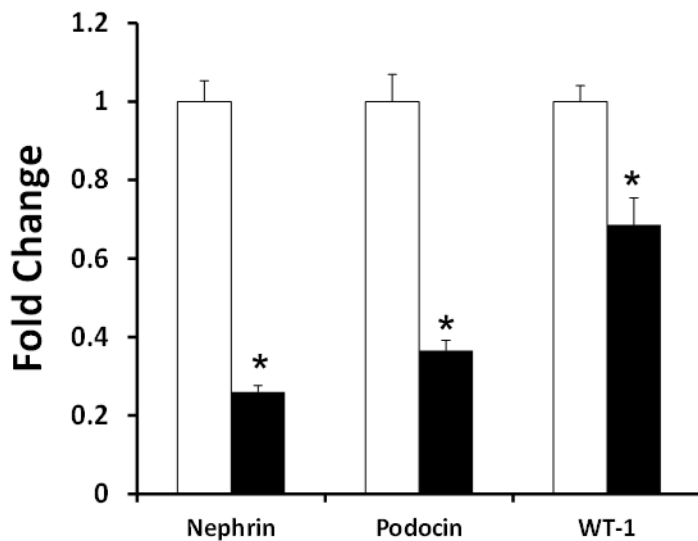
**Supplementary Figure 3:** Ultrastructural changes in ReninAAV *db/db* uNx mice. (A) Quantitative measurement of glomerular basement membrane thickening from TEM images (\* $p < 0.01$  compared to *db/m*,  $\$p < 0.01$  compared to *db/db* uNx controls). (B) ReninAAV *db/db* uNx mice exhibited marked basement membrane splitting and reduplication characterized by subendothelial expansion by amorphous material, infoldings and mesangial interposition (11500x magnification, bar = 1  $\mu\text{m}$ ). Arrows highlighting basement membrane splitting and duplication.

Supplementary Figure 4:

A)

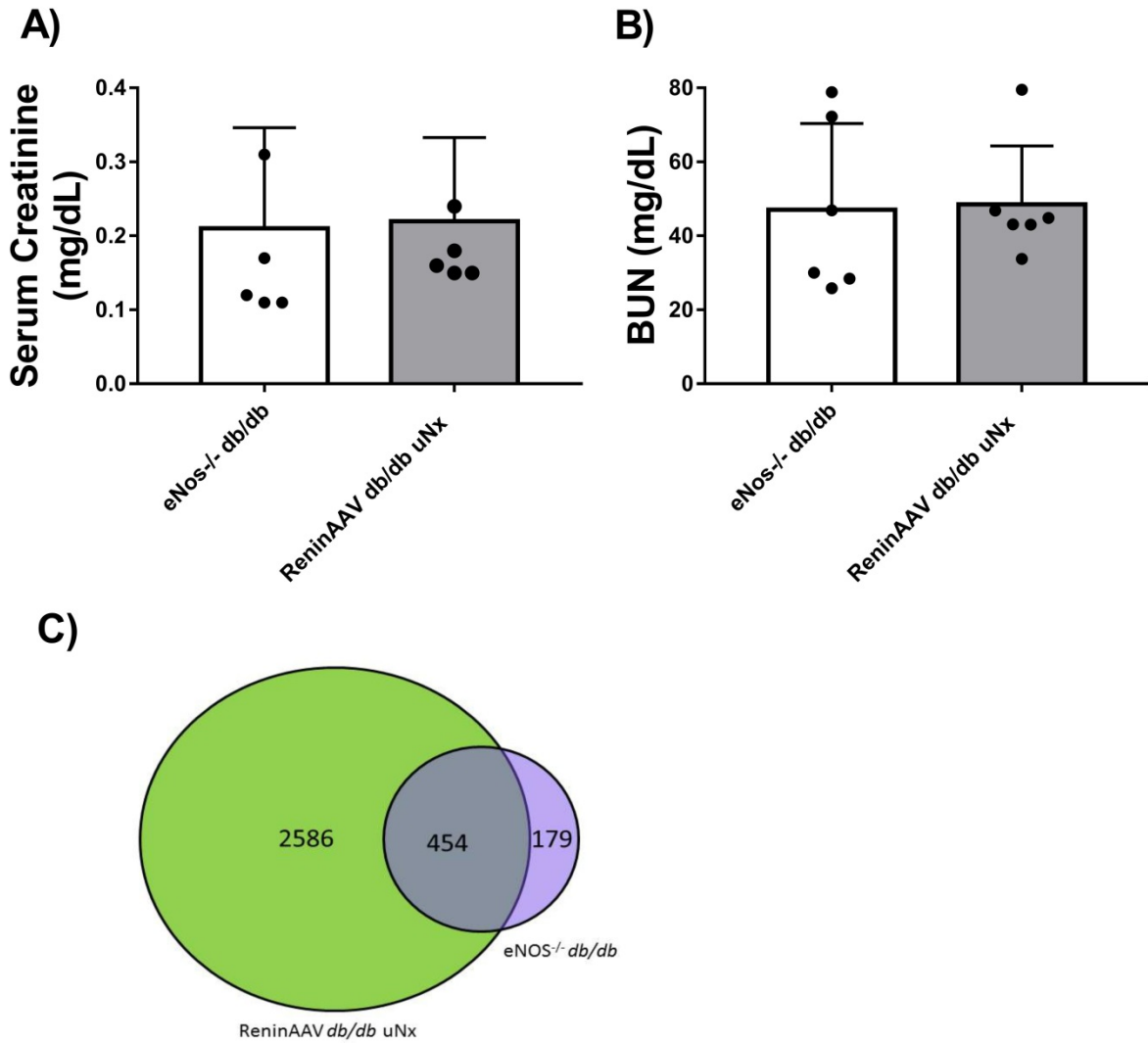


B)



**Supplementary Figure 4:** Gene expression analysis by microarray (Col4A1 and Col4A2) or taqman (FN1, TGFβ, Nephrin, Podocin, and WT-1) of ReninAAV *db/db* uNx mice as compared to LacZAAV *db/db* uNx controls. (A) Increased Col4a1 and Col4a2 support increased mesangial matrix expansion observed in ReninAAV *db/db* uNx mice. Markers of fibrosis, fibronectin and TGFβ were elevated in the ReninAAV *db/db* uNx mice. (B) Podocyte specific markers were lower in the ReninAAV *db/db* uNx mice as compared to LacZ *db/db* uNx controls suggesting podocyte loss in the model. \*p<0.05

Supplementary Figure 5:



**Supplementary Figure 5:** Clinical parameters from *ReninAAV db/db uNx* and *eNOS<sup>-/-</sup> db/db* mice selected for microarray analysis comparison. Serum creatinine (A) and blood urea nitrogen (BUN)(B) were not statistically different ( $p=0.44$  and  $0.45$  respectively) between the two cohorts of mice selected for analysis. (C) Venn diagram demonstrating number of gene changes unique to *ReninAAV db/db uNx* and *eNOS<sup>-/-</sup> db/db* models as well as number of shared gene changes.