Effect of lisinopril on glomerular and tubular injury in a surgical rat model of progressive chronic kidney disease and kidney failure

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Background & Aim

The 5/6 nephrectomy (Nx) rat model of CKD displays progressive albuminuria, glomerulosclerosis, tubulointerstitial fibrosis, and loss of kidney function. Here, we characterised the effect of lisinopril, a standard ACE inhibitor, on kidney histopathology, renal biochemical markers, and kidney function in 5/6 Nx rats.

Methods

Male Wistar rats (9 wks old) underwent sham operation or 2/3 nephrectomy at week -4 and Nx at week -2. Rats were randomised based on plasma urea, creatinine, and BW. 5/6 Nx rats received vehicle or Lisinopril (20 mg/kg, PO, QD), for 8 weeks. The albumin-to-creatinine ratio (ACR) was measured at week 7 and the glomerular filtration rate (GFR) at week 8. Terminal plasma was sampled for urea, creatinine and cholesterol. The remaining kidney was harvested for quantitative histological assessment of glomerulosclerosis (PAS staining), macrophage infiltration (CD68), tubular injury (KIM-1), and fibrosis (Col1a1).

Conclusion

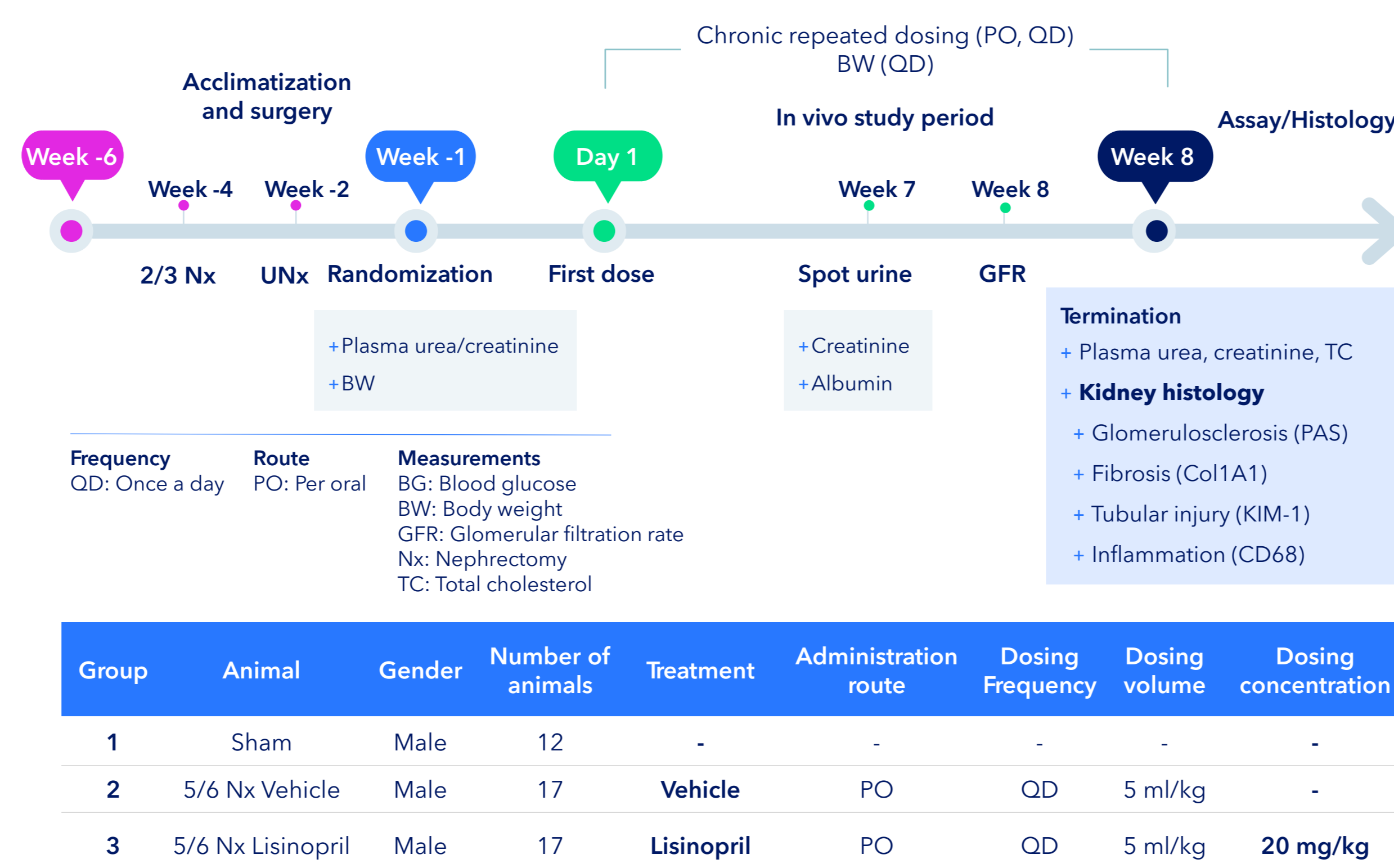The present study in 5/6 Nx rats establishes that lisinopril

+ Improves albuminuria

+ Reduces tubular injury

+ Reduces renal inflammation

These findings support nephroprotective effects of lisinopril in CKD and highlights the applicability of the 5/6 Nx rat model in preclinical drug development.
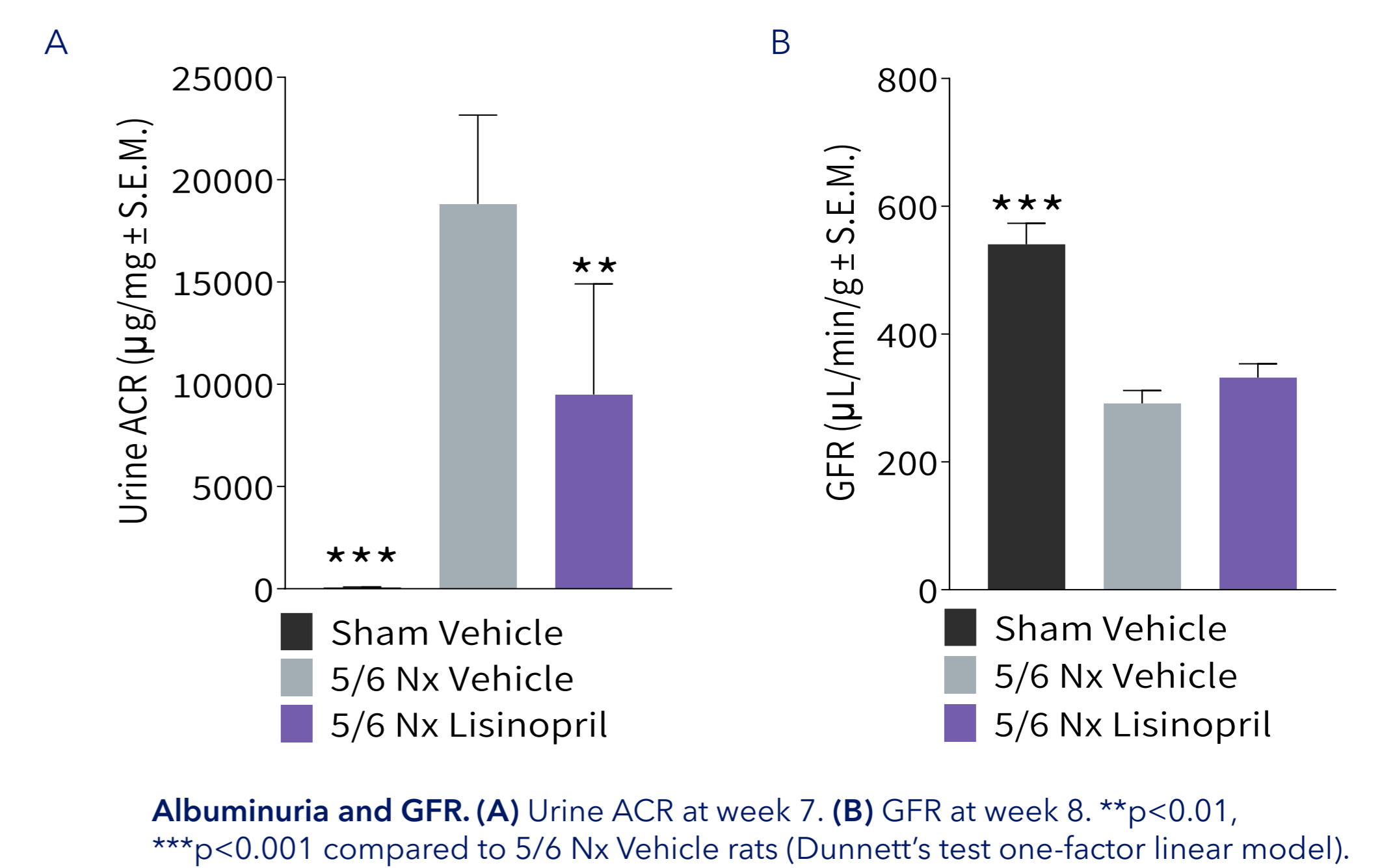
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1 Study outline

| Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing volume	Dosing concentration
1	Sham	Male	12	-	-	-	-	-
2	5/6 Nx Vehicle	Male	17	**Vehicle**	PO	QD	5 ml/kg	-
3	5/6 Nx Lisinopril	Male	17	**Lisinopril**	PO	QD	5 ml/kg	**20 mg/kg**

2 Albuminuria and GFR

Albuminuria and GFR. (A) Urine ACR at week 7. **(B)** GFR at week 8. **p<0.01, ***p<0.001 compared to 5/6 Nx Vehicle rats (Dunnett's test one-factor linear model).

3 Plasma creatinine and urea
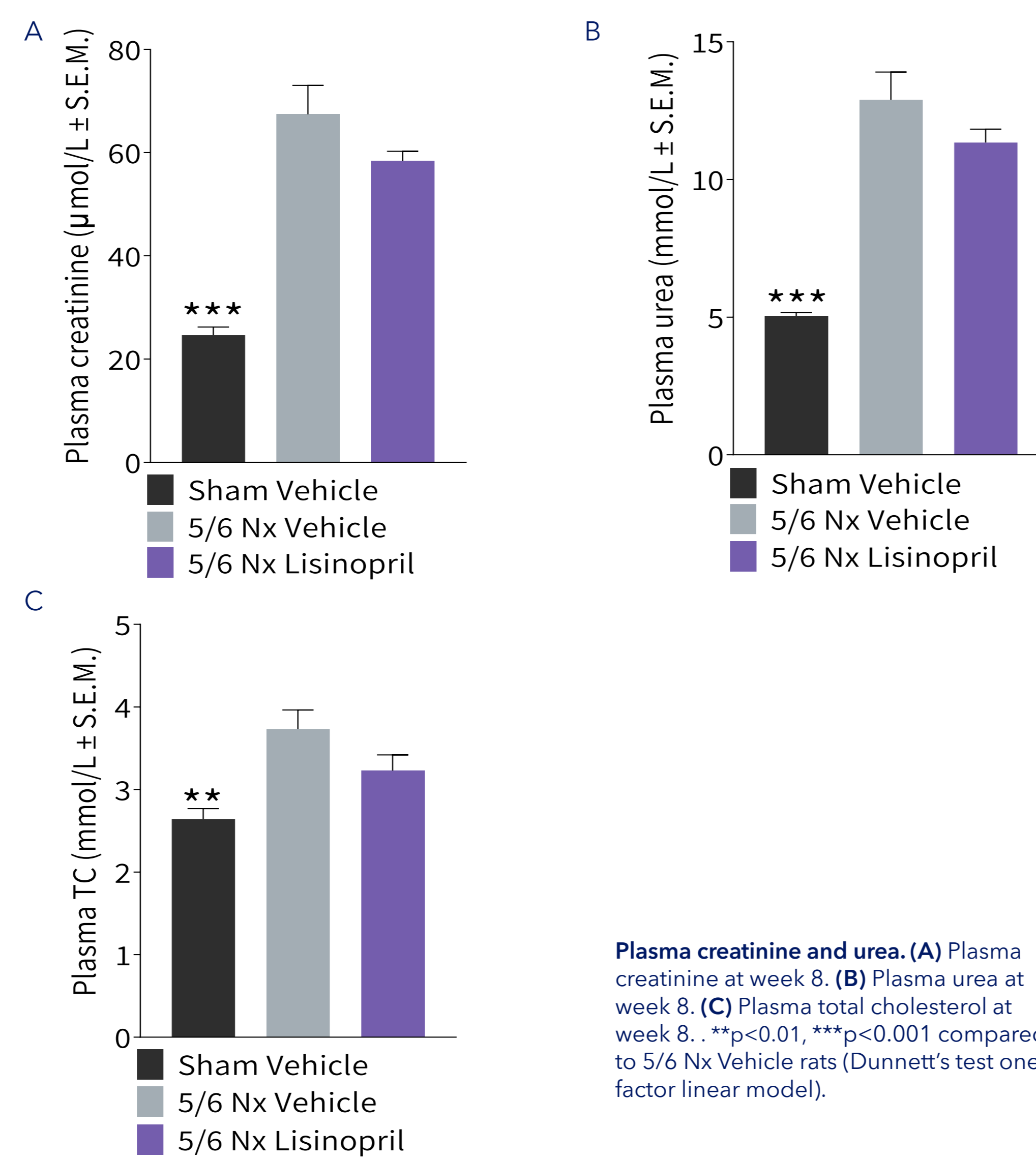
Plasma creatinine and urea. **(A)** Plasma creatinine at week 8. **(B)** Plasma urea at week 8. **(C)** Plasma total cholesterol at week 8. . **p<0.01, ***p<0.001 compared to 5/6 Nx Vehicle rats (Dunnett's test one-factor linear model).

4 Glomerulosclerosis
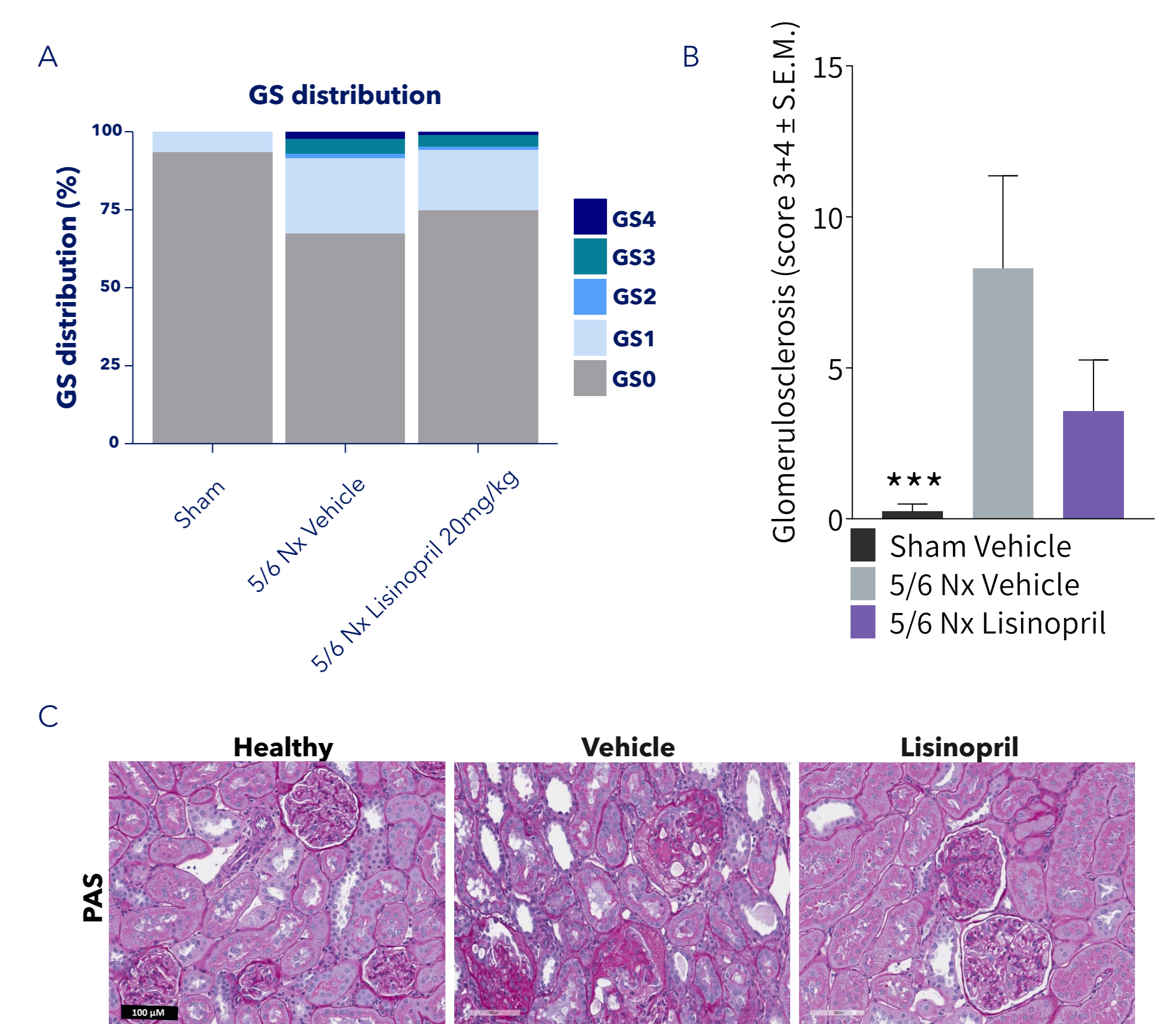
Glomerulosclerosis. The percentage of animals with score 0 (normal), score 1 (up to 25% involvement), score 2 (up to 50% involvement), score 3 (up to 75% involvement), and score 4 (global, more than 75% involvement). **(A)** Distribution of all scores. **(B)** Glomerulosclerosis score 3 and 4 (mean ±S.E.M.) **(C)** Representative photomicrographs (scale bar, 100 µm). ***p<0.001 compared to 5/6 Nx Vehicle rats (Dunnett's test one-factor linear model).

5 Histological markers of kidney injury
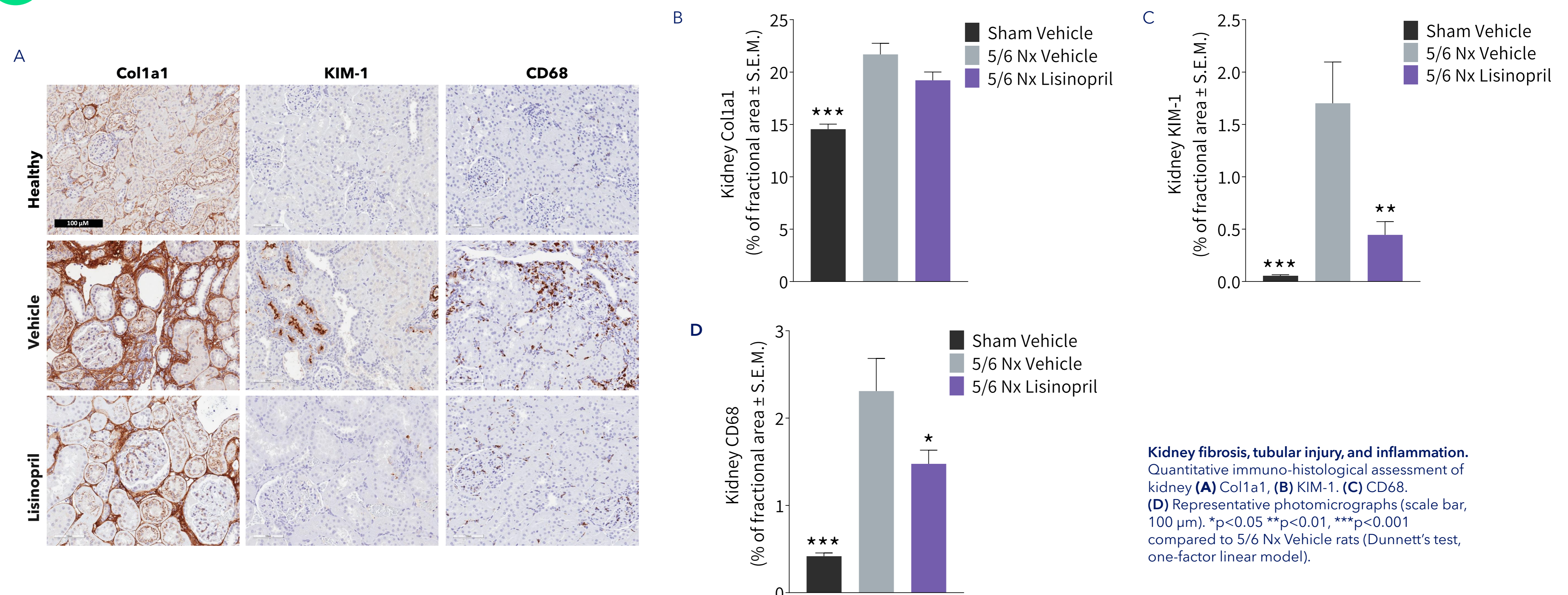
Kidney fibrosis, tubular injury, and inflammation. Quantitative immuno-histological assessment of kidney **(A)** Col1a1, **(B)** KIM-1. **(C)** CD68. **(D)** Representative photomicrographs (scale bar, 100 µm). *p<0.05 **p<0.01, ***p<0.001 compared to 5/6 Nx Vehicle rats (Dunnett's test, one-factor linear model).