

# OXIDATIVE/NITRATIVE STRESS AND INFLAMMATION DRIVE PROGRESSION OF DOXORUBICIN INDUCED RENAL FIBROSIS IN RATS AS REVEALED BY COMPARING A NORMAL AND A FIBROSISRESISTANT RAT STRAIN

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## Background

• Rowett, black hooded (BH) rats - resistant to renal fibrosis (G. Kökény, P. Hamar, NDT, 2009)  
• We compared renal damage of CD and BH rats in the doxorubicin (DXR)-induced nephropathy model.

## Materials and methods:

### Groups:

#### a. Survival:

- CD/DXR (5mg/kg)
- BH/DXR (5mg/kg)



Charles - Dawley (CD) rat

#### b. Functional:

- CD/c (saline)
- CD/DXR (5 mg/kg)
- BH/c (saline)
- BH/DXR (5 mg/kg)



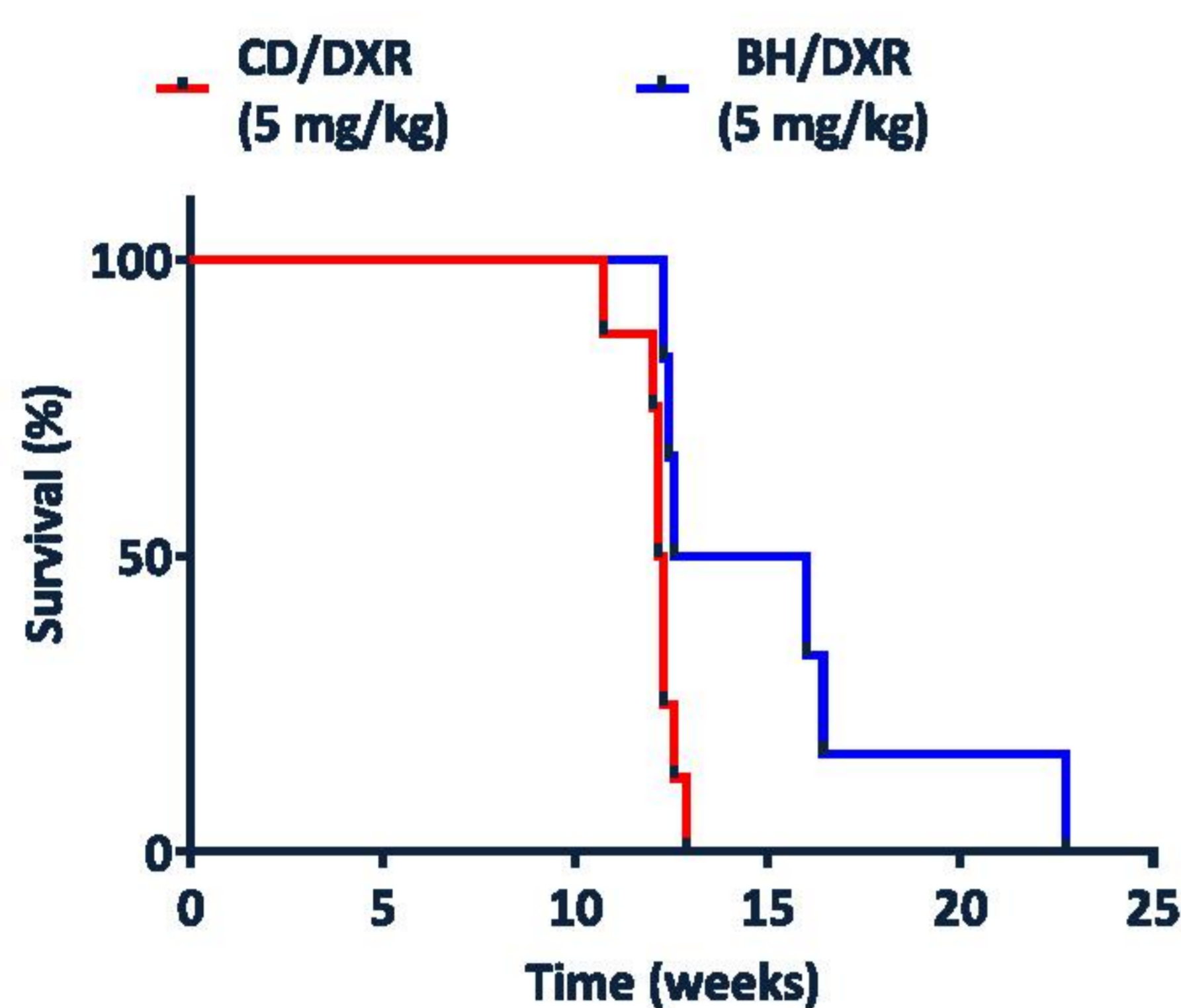
Rowett Black Hooded (BH) rat

### Statistics:

Mann-Whitney U-test, two-way ANOVA and repeated measures ANOVA were used.  
All values were expressed as means +/- SEM.

## Results:

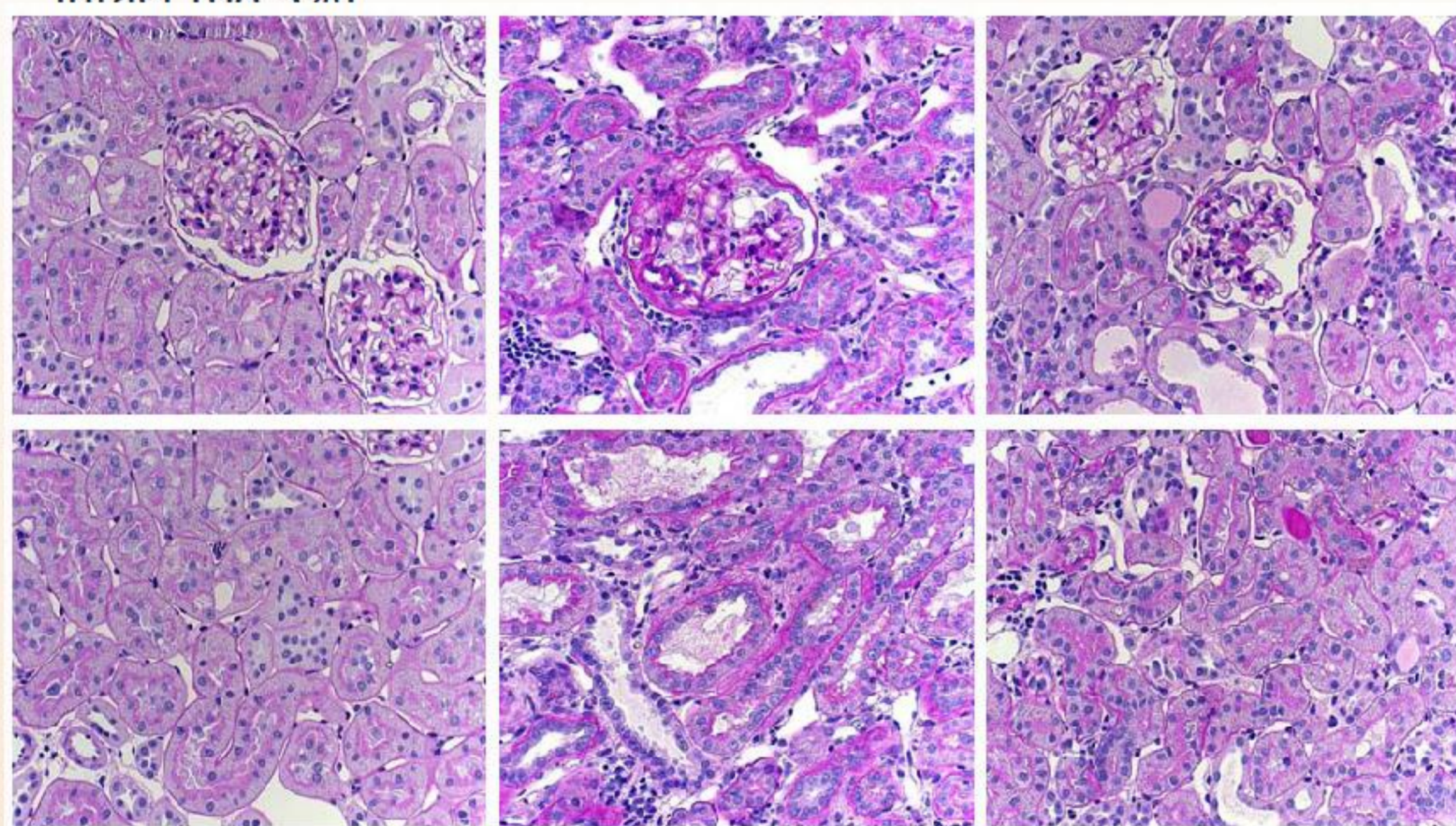
### The survival rate of BH and CD rats



### Renal morphology

#### DXR injected BH and CD rats

DXR treated BH rats had milder glomerular damage and tubular damage compared to CD rats.  
In the DXR injected CD rats 41.9% of the glomeruli were intact, in the DXR treated BH rats, more glomeruli stayed intact (68.3%)



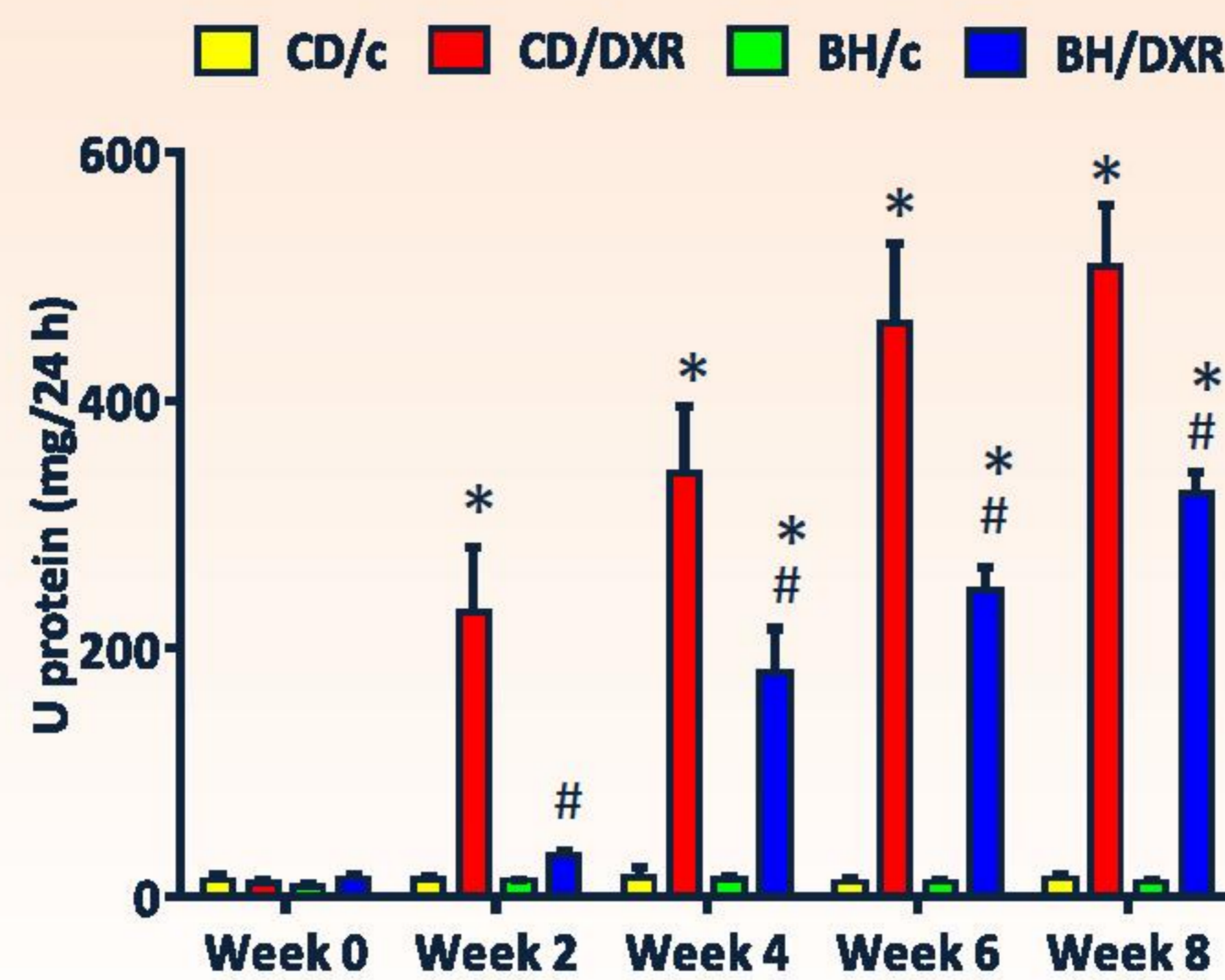
#### Upper panel:

Glomerular damage: A: Saline control, B: CD-DXR, C: BH-DXR

#### Lower panel:

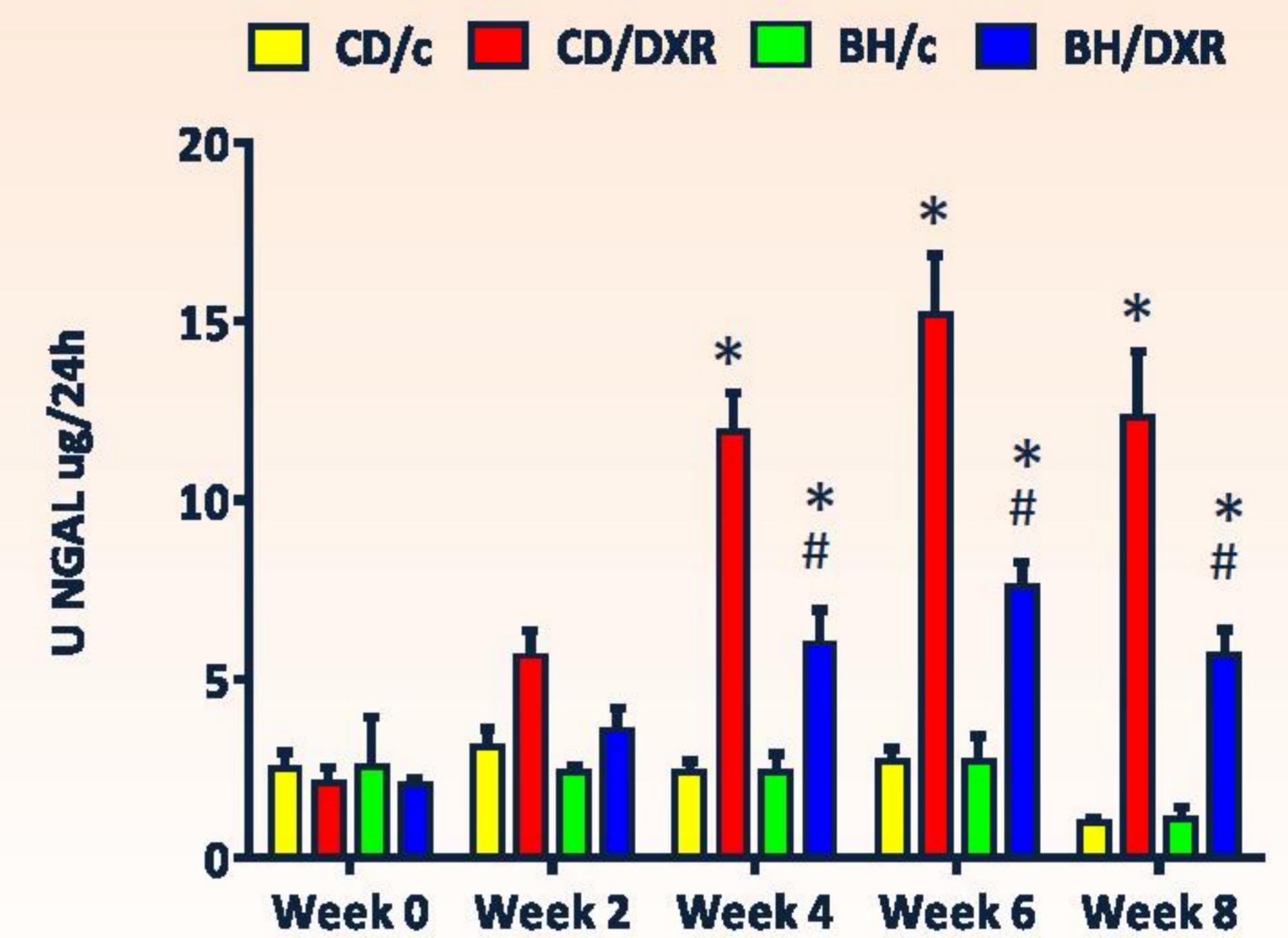
Tubular damage: D: Saline control, E: CD-DXR, F: BH-DXR

### Urinary protein excretion

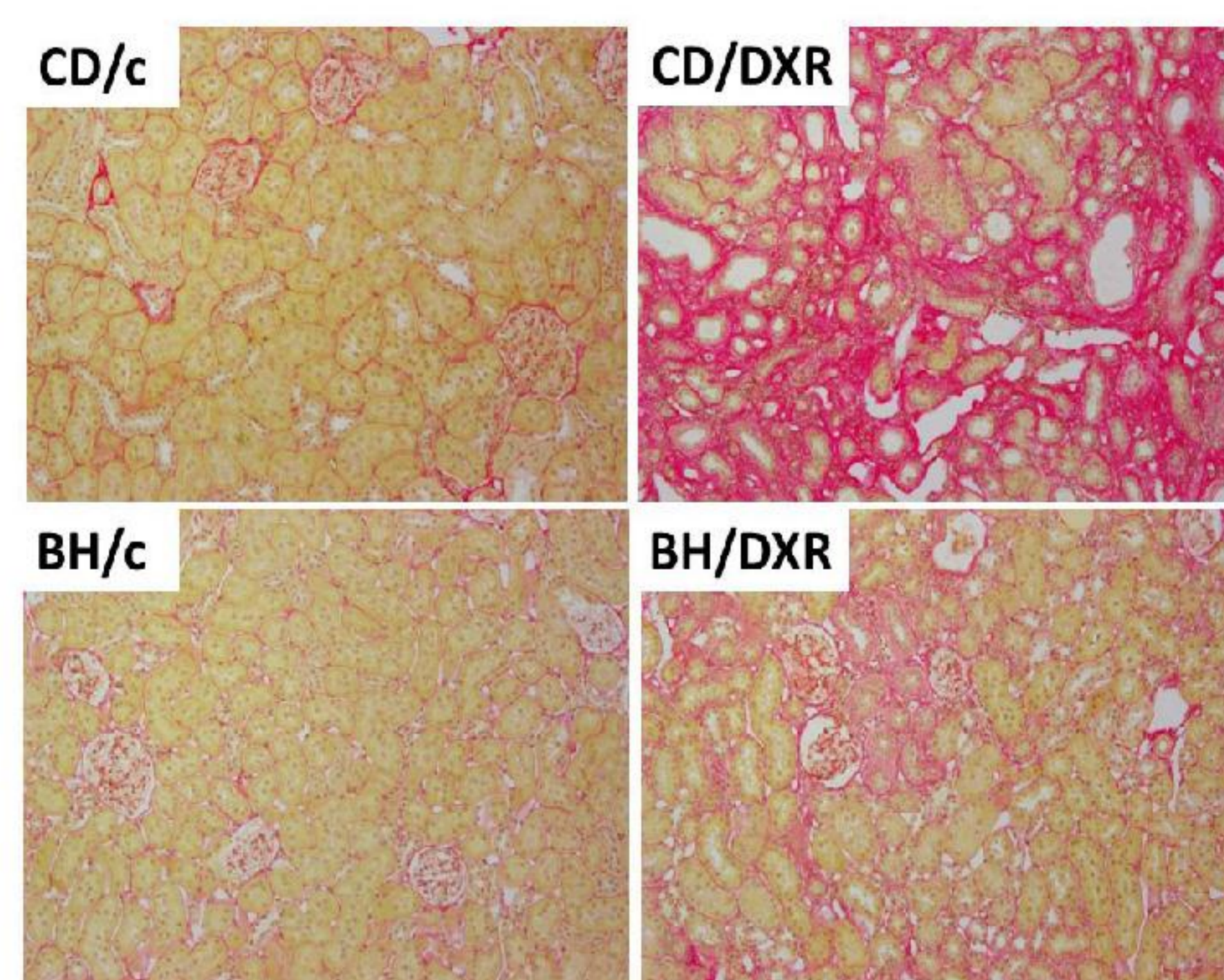


\*: p<0.05 vs. strain-identical, negative control group, #: p<0.05 vs. CD/DXR, positive control group.

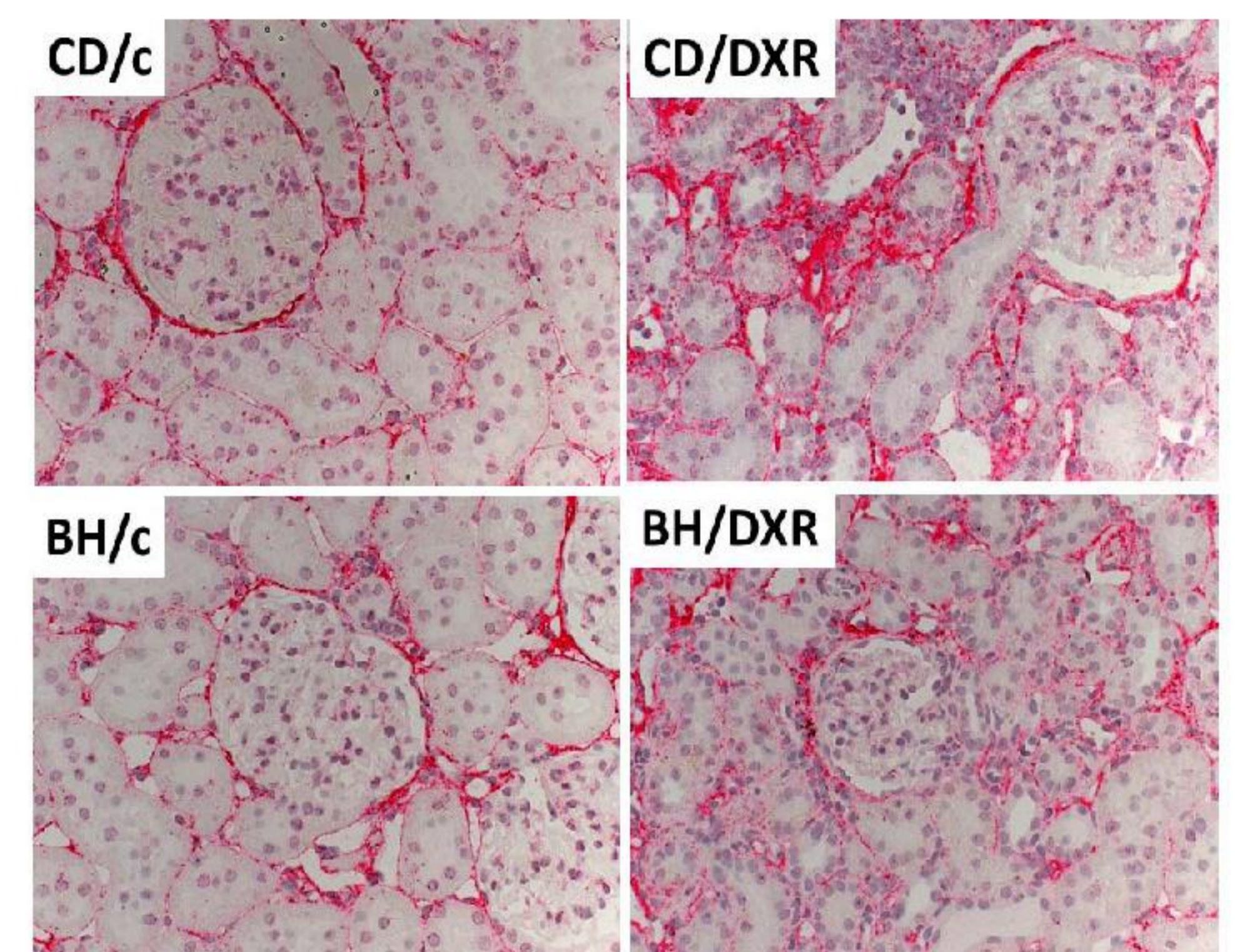
### Urinary NGAL excretion



### Picro-Sirius red staining in the kidney cortex

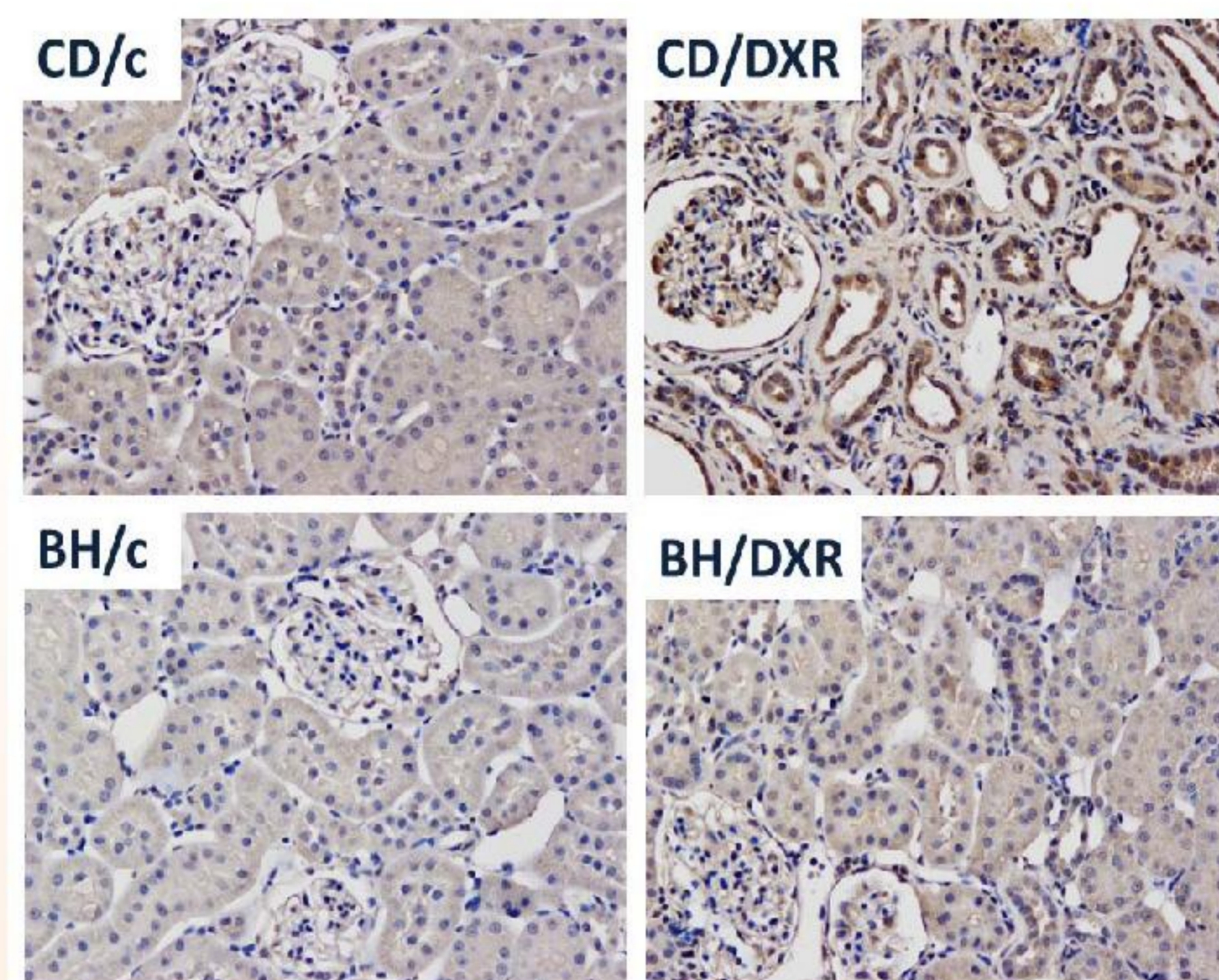


### Fibronectin staining in the kidney cortex

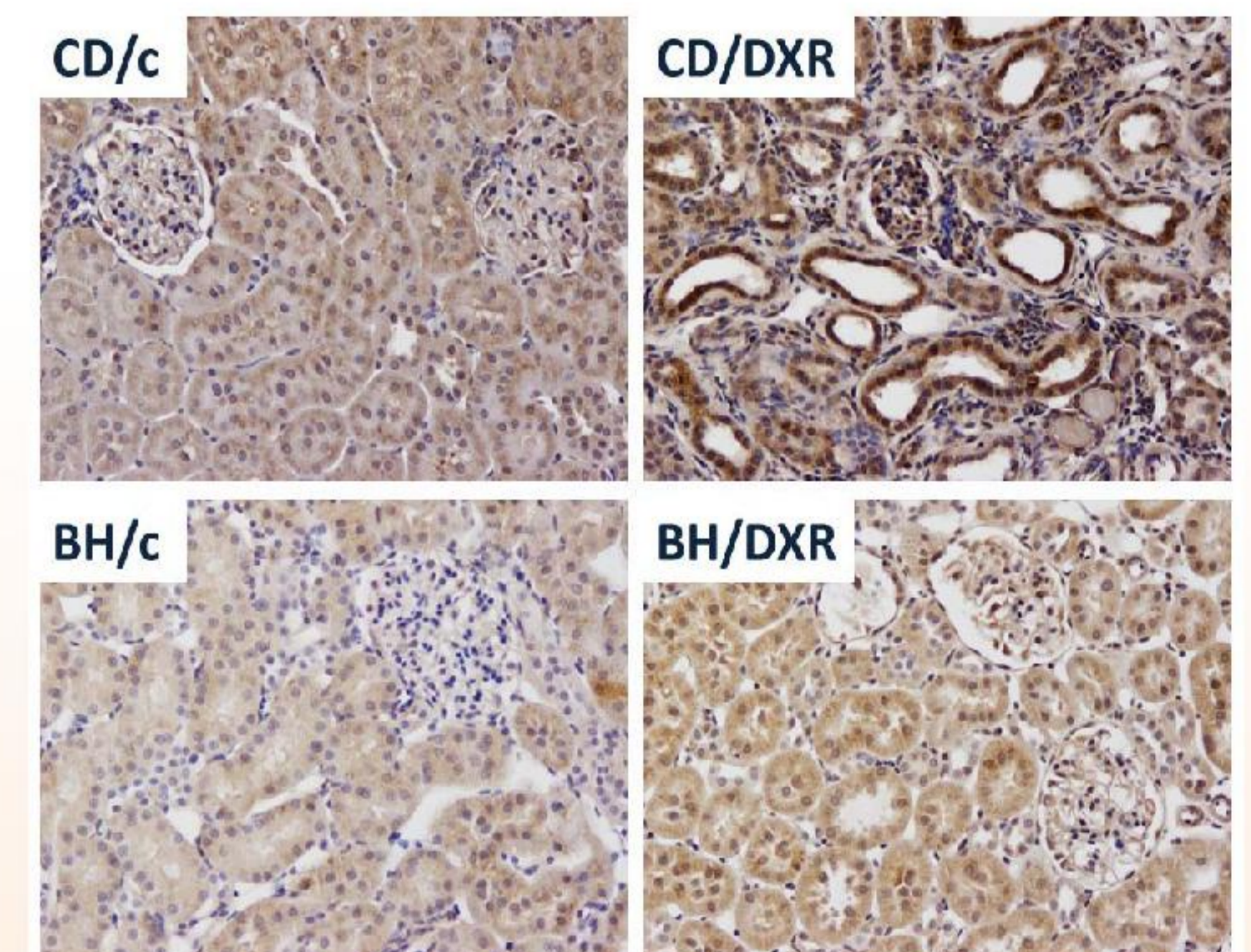


	CD/c	CD/DXR	BH/c	BH/DXR
Stained area (%)				
Picro-Sirius red	3.78 +/- 1.36	23.48 +/- 8.53 *	1.96 +/- 0.44	9.69 +/- 5.41 *#
Fibronectin	5.38 +/- 0.49	8.39 +/- 2.19 *	5.08 +/- 0.75	6.04 +/- 1.3 #
Mean +/- SD, n=10/group				

### 4-Hydroxynonenal renal cortex



### Nitrotyrosine renal cortex



### Gene expression renal cortex CD / BH rats

	CD/c	CD/DXR	BH/c	BH/DXR
Nephrin	1.15 +/- 0.19	0.60 +/- 0.19 *	1.04 +/- 0.06	0.89 +/- 0.19 #
TGF-β1	1.00 +/- 0.32	5.16 +/- 2.06 *	1.00 +/- 0.20	1.68 +/- 0.98 #
CTGF	1.00 +/- 0.28	3.32 +/- 1.60 *	1.00 +/- 0.43	0.70 +/- 0.31 #
COL1A1	1.00 +/- 0.78	19.89 +/- 6.93 *	1.00 +/- 0.20	4.33 +/- 2.38 **
p47 phox	1.00 +/- 0.26	3.75 +/- 1.65 *	1.00 +/- 0.13	1.93 +/- 0.43 **
p91 phox	1.00 +/- 0.55	9.13 +/- 3.74 *	1.00 +/- 0.31	2.30 +/- 0.81 *#
MCP-1	1.00 +/- 0.17	8.34 +/- 3.07 *	1.00 +/- 0.37	3.19 +/- 0.87 **

Mean +/- SD, n=10/group

\*: p<0.05 vs. strain-identical, negative control group, #: p<0.05 vs. CD/DXR, positive control group.

**In conclusion,** resistance of BH rats against renal fibrosis highlighted the role of inflammatory response induced oxidative/nitrative stress in podocyte injury leading to glomerulosclerosis and consequent proteinuria in DXR nephropathy.

**Abbreviations:** NGAL: neutrophil gelatinase associated lipocalin, HNE: 4-hydroxynonenal, NT: nitrotyrosine, TGF-β: transforming growth factor β1, CTGF: connective tissue growth factor, COL1A1: collagen type 1 alpha 1, MCP1: monocyte chemotactic protein-1.

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