Febuxostat prevents diabetic renal injury by attenuating inflammation and oxidative stress

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BACKGROUND

- Oxidative stress and inflammation are known to play a central role in the development of diabetic nephropathy.
- Febuxostat (Fx) is a novel nonpurine xanthine oxidase (XO)-specific inhibitor for treating hyperuricemia.
- The reduction in oxidative stress by administering the XO inhibitor has been shown to slow the progression of renal dysfunction.
- The renoprotective effects of an XO inhibitor have been suggested as uric acid lowering effect and anti-inflammatory effect.
- In this study, we investigated whether Fx could attenuate diabetic kidney injury and impart renoprotective effects, including anti-oxidative stress and anti-inflammatory mechanisms.

METHODS

- Male Sprague–Dawley rats were divided into three groups:
  - ✓ normal
  - ✓ vehicle-treated diabetes (DM)
  - ✓ febuxostat-treated diabetes (DM+Fx).
- We administered 5mg/kg of Fx to experimental rats for 7 weeks.
- We evaluated clinical and biochemical parameters and XO and xanthine dehydrogenase (XDH) activity in hepatic tissue.
- The degree of oxidative stress and inflammation were evaluated from urine samples and renal tissue collected from each group.

RESULTS

Table 1. Effect of febuxostat on clinical parameters

Variables	Group		
	Normal (N=7)	DM (N=6)	DM + Fx (N=7)
KW/BW ratio (X 1000)	5.23±0.64	8.42±1.11*	9.07±1.35*
pGlucose (mg/dL)	110.6±4.69	548.4±13.02*	544.1±19.21*
Urine vol (mL/24hrs)	6.75±1.18	15.20±5.16*	15.98±3.85*
ACR (X 100)	0.79±0.59	2.74±0.56*	0.92±0.35#
pCreatinine (mg/dL)	0.42±0.04	0.47±0.02	0.56±0.12
pUric acid (mg/dL)	0.94±0.16	0.82±0.10	0.71±0.20

* $P< 0.05$ compared with the normal group. # $P< 0.05$ compared with the diabetic group

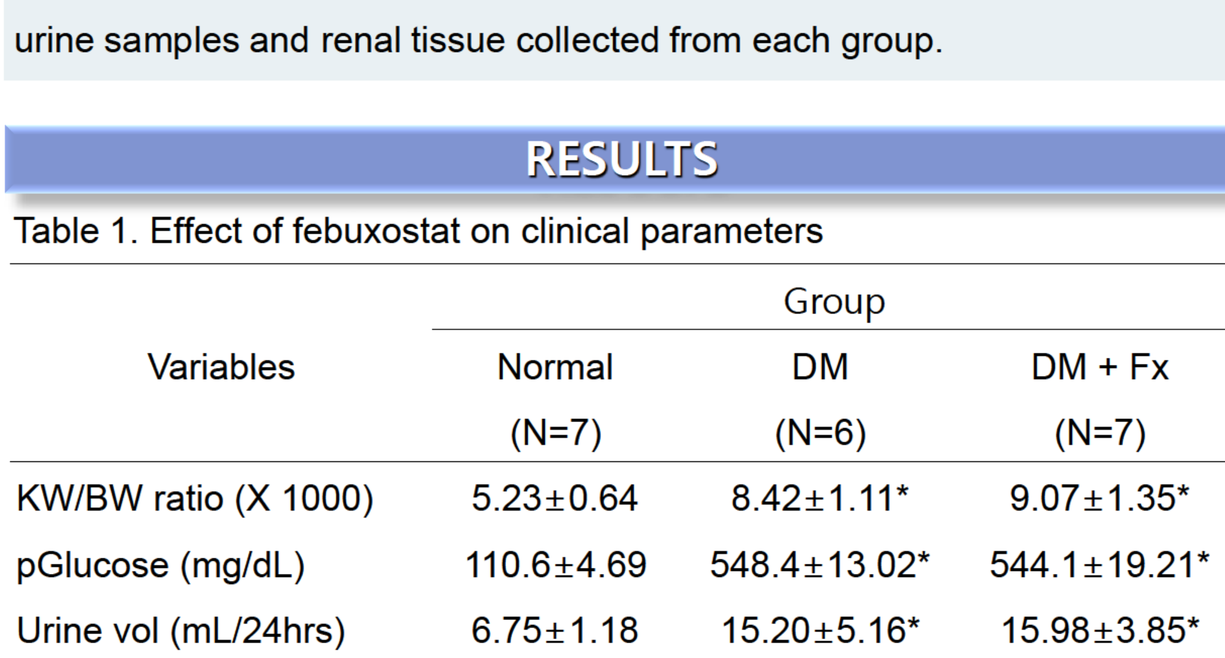

Figure 1. Immunohistochemistry for ED-1 in glomerulus (A)(C)and tubule (B)(D).

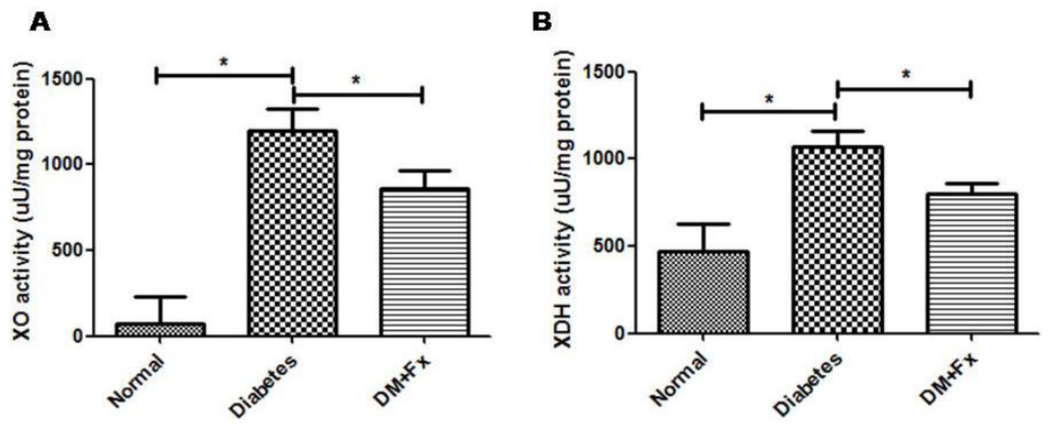

Figure 2. Effects of diabetes and treatment with Fx on hepatic XO and XDH

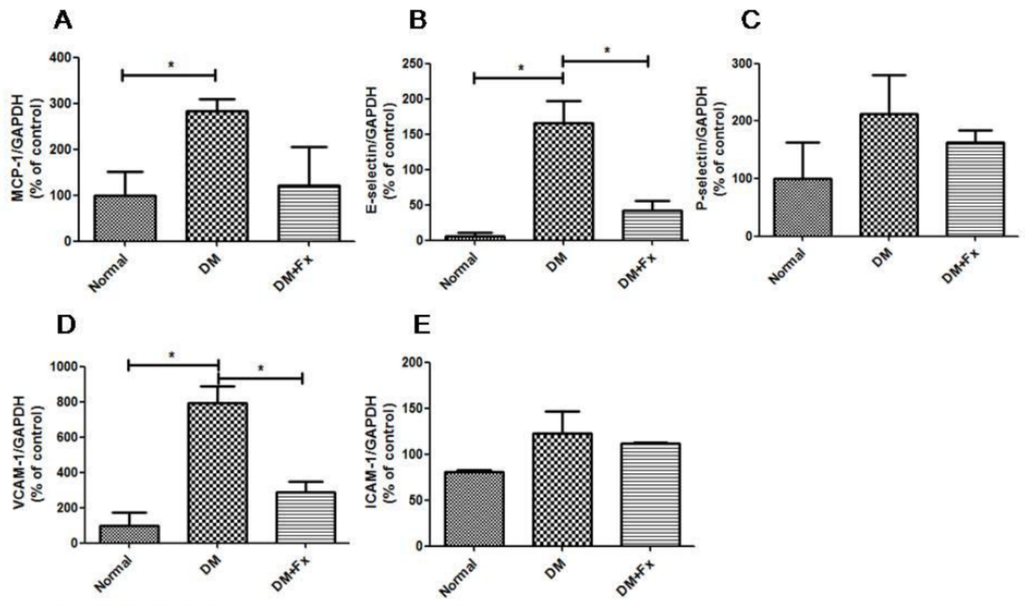

Figure 3. RT-PCR analysis of mRNA from the renal cortex of each group.

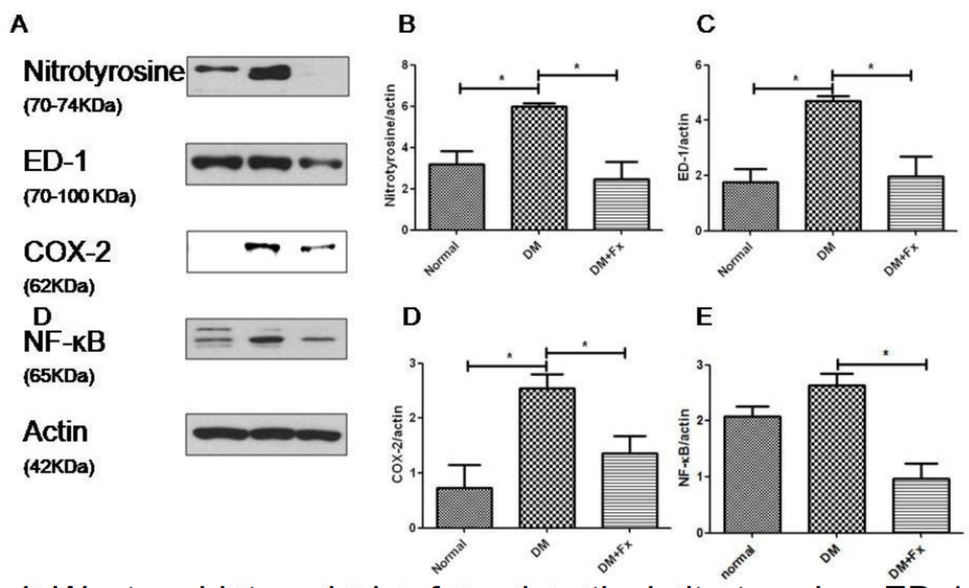

Figure 4. Western blot analysis of renal cortical nitrotyrosine, ED-1, COX-2 and NF-κB.

SUMMARY

- Urinary albuminuria was significantly reduced in Fx-treated diabetic rats.
- Renal cortical nitrothyrosine also indicated reduced oxidative stress in the DM+Fx group relative to the DM group.
- Quantitative analysis showed that hepatic XO and XDH activity was increased in the DM group (DM and DM+Fx groups) but reduced after treatment with Fx.
- We also observed a greater number of ED-1 stained cells in the glomerulus and tubule of diabetic renal tissue compared to normal; after administration of Fx, ED-1 stained cell count decreased.
- Finally, diabetic rats showed increased mRNA expression of inflammatory genes(E-selectin and VCAM-1), inflammation inducible enzymes(COX-2), and inflammatory mediators(ED-1 and NF-kB): after administration of Fx, these showed decreased significantly.

CONCLUSION

- Febuxostat ameliorates the diabetic renal injury such as albuminuria.
- Renoprotective effects of Fx may attenuate the inflammatory and oxidative stress mechanisms of renal damage in diabetes by inhibiting XO and XDH activity.

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