PIOGLITAZONE EFFECTIVELY REDUCES RENAL INTERSTITIAL FIBROSIS IN TGF-ß TRANSGENIC MICE

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BACKGROUND

Peroxisome proliferator-activated receptor-γ (PPARγ) agonists (pioglitazone, troglitazone) have been shown to reduce renal fibrosis in animal models of diabetic nephropathy, ischemia reperfusion injury or autosomal dominant polycystic kidney disease.
There are, however, conflicting results regarding the antifibrotic effect of PPARγ agonists in unilateral ureter obstruction induced kidney fibrosis models (1,2). Thus, the relationship between PPAR-γ and tubulointerstitial fibrosis is not clear yet.
TGF-ß1 plays a pivotal role in fibrosis by regulating profibrotic genes. TGF-ß transgenic mice have elevated plasma TGF-ß1 levels (3) We have previously shown that alb/TGF-ß1 transgenic mice (TGFb) on C57Bl6/J (B6) genetic background develop progressive glomerulosclerosis and renal interstitial fibrosis (3,4).

In the present study, we aimed to investigate whether chronic treatment with PPARγ agonist pioglitazone could counteract the profibrotic renal effect of elevated circulating TGF-β in transgenic mice.

METHODS

Animal model:
Ten week old male C57Bl6 control and TGF-β transgenic mice were divided in two sets. The first set of mice received regular chow (Control and TGFb).
The second set of mice were treated orally with pioglitazone (20mg/kg/day) for 5 weeks (Control+Pio and TGFb+Pio).

Experimantal groups:
1) Control (n=4)
2) TGFb (n=4)
3) C+Pio (20mg/kg/day pioglitazone, n=7)
4) TGFb+Pio (20mg/kg/day pioglitazone, n=10)

At 15 weeks of age, spot urine sample was obtained and kidneys were analyzed.

Performed analyses:

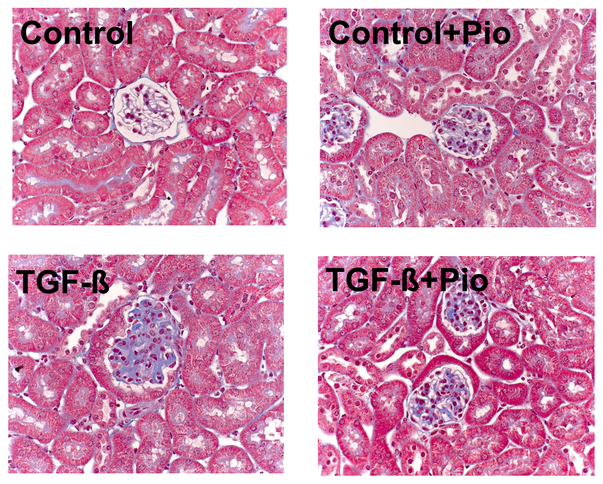
- Urinary protein/creatinine ratio
- Renal histology
- Renal mRNA expression of
  - collagen-III,
  - TGF-ß
  - TIMP-1

Statistics:
Data are presented as mean±SD. Statistical significance was analyzed using two-way ANOVA followed by Sidak's multiple comparison test.

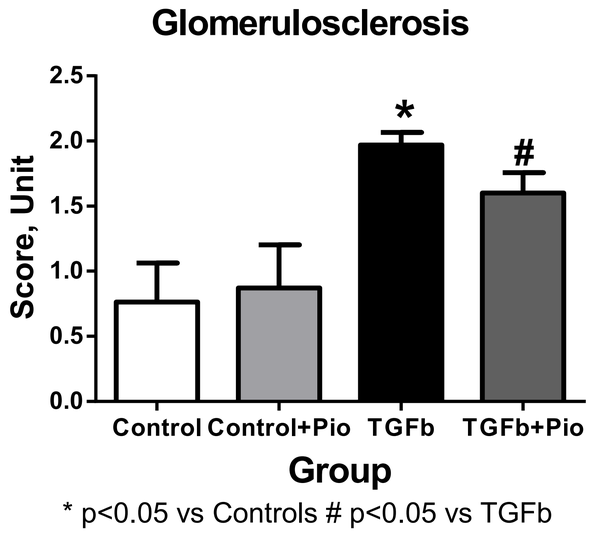
RESULTS

Renal histology

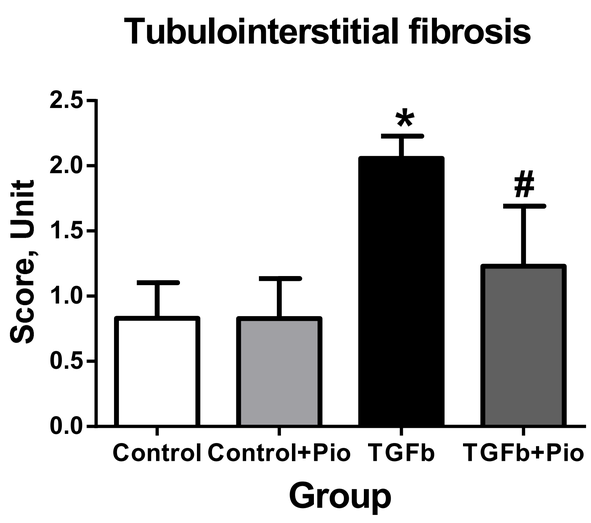
Pioglitazone successfully reduced the TGF-ß induced glomerular- and tubulointerstitial fibrosis.



Masson's trichrome stain, 400x magnification (blue: connective tissue)



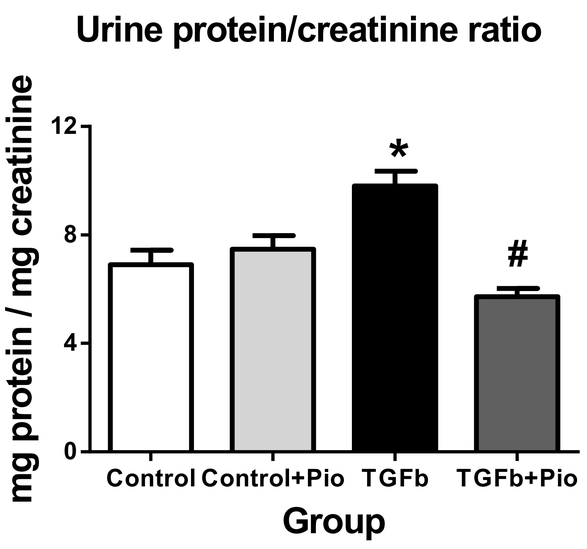
* p<0.05 vs Controls # p<0.05 vs TGFb



* p<0.05 vs Controls # p<0.05 vs TGFb

Proteinuria

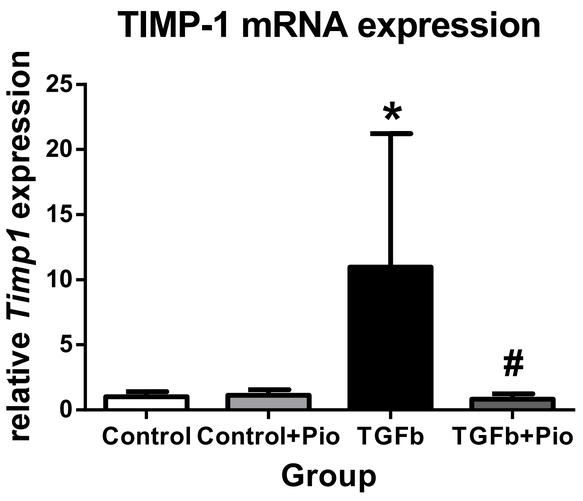
Pioglitazone treatment significantly reduced urine protein/creatinine ratio to normal levels.



* p<0.05 vs Controls # p<0.05 vs TGFb

Gene expression

Pioglitazone treatment inhibited the overexpression of both TIMP-1 and type-III collagen mRNA.



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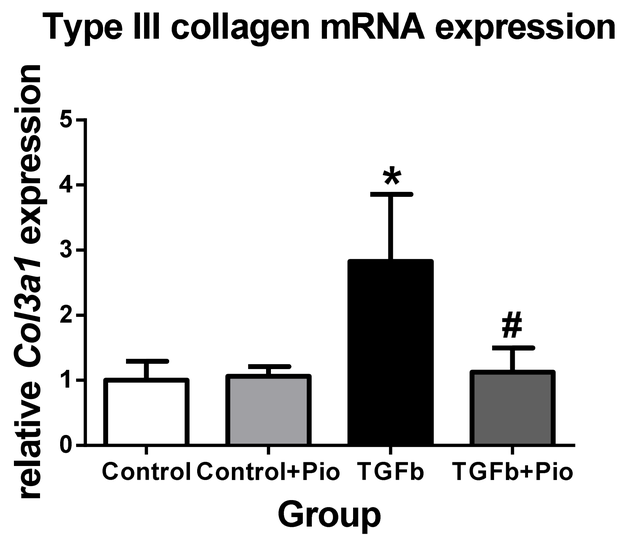

* p<0.05 vs Controls # p<0.05 vs TGFb

CONCLUSION

We conclude that chronic pioglitazone administration can effectively reduce the profibrotic effect of elevated circulating TGF-ß in the renal interstitium, and to less extent in the glomeruli. Our results might help to clarify the relationship between PPAR-g and tubulointerstitial fibrosis.

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