

## PIOGLITAZONE REDUCES RENAL FIBROSIS IN A RAT MODEL OF TYPE 2 DIABETES

<sup>1</sup>Toblli Jorge; <sup>2</sup>Ferrini Monica G, <sup>1</sup>Cao Gabriel, <sup>2</sup>Vernet Dolores, <sup>1</sup>Angerosa Margarita <sup>2</sup>Gonzalez Cadavid Nestor F. <sup>1</sup>Lab. of Experimental Medicine. Hospital Alemán. Buenos Aires, Argentina. <sup>2</sup>LABioMed at Harbor-UCLA Medical Center. Torrance, CA, USA.

Peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) agonists are used in patients with type 2 diabetes or metabolic syndrome. Although some studies have suggested a beneficial effect on kidney function, its mechanism is still unclear. In this study we aimed to evaluate whether a PPAR $\gamma$  agonist, pioglitazone (PGT), protects from renal fibrosis in Obese Zucker rats fa/fa (OZR-fa/fa), a rat model of insulin resistance. Male rats, 2.5 month old (n=8/group) received regular chow or chow with PGT at low dose (LD: 0.6 mg/kg) or high dose (HD: 12 mg/kg), for 2 or 5 months, as indicated on the table, plus a 2 months-HD group. Masson's trichrome, alpha-smooth muscle actin (SMA) as myofibroblast marker, TGF $\beta$ 1 (pro-fibrotic factor) and collagen I and III were measured by quantitative image analysis/immuno-histochemistry. In addition, collagen was estimated by hydroxyproline, calponin and also SMA by western blots. Glomerulosclerosis (GS); Interstitial Fibrosis (IF); and Tubular Atrophy (TA) were also evaluated.

% Mean $\pm$ SD	Lean Zucker Rat 5 months	OZR-fa/fa, 2 months	OZR-fa/fa, 5 months	OZR-fa/fa-LD 2 months	OZR-fa/fa-LD 5 months
GS	*0.9 $\pm$ 0.5	*19.4 $\pm$ 3.9	*28.7 $\pm$ 6.5	†12.9 $\pm$ 2.0	6.9 $\pm$ 1.8
IF	*2.6 $\pm$ 1.1	*12.1 $\pm$ 1.8	*16.9 $\pm$ 2.8	†9.9 $\pm$ 1.8	6.8 $\pm$ 1.1
TA	*1.7 $\pm$ 0.8	*7.3 $\pm$ 1.5	*9.2 $\pm$ 1.8	†6.4 $\pm$ 0.9	4.5 $\pm$ 0.8
SMA	*1.3 $\pm$ 0.5	*11.9 $\pm$ 1.5	*14.1 $\pm$ 1.2	†7.1 $\pm$ 1.3	4.8 $\pm$ 0.9
TGF $\beta$ 1	*1.8 $\pm$ 0.4	*24.3 $\pm$ 2.3	*26.7 $\pm$ 3.0	†14.8 $\pm$ 2.7	9.7 $\pm$ 1.8
Col-III	*4.6 $\pm$ 0.5	*13.4 $\pm$ 1.9	*17.2 $\pm$ 1.8	†10.2 $\pm$ 1.6	7.8 $\pm$ 1.5
Col-I	*1.1 $\pm$ 0.4	*9.6 $\pm$ 1.6	*12.3 $\pm$ 1.4	†6.5 $\pm$ 0.7	5.2 $\pm$ 0.5

\*vs all groups  $p < 0.01$ ; † vs OZR-fa/fa, 5 months low  $p < 0.01$ .

PGT-LD treatments for 2 and 5 months and PGT-HD for 2 months significantly reduced myofibroblast formation, collagen deposition, and other fibrotic indexes in the kidney without affecting smooth muscle content (calponin). In conclusion, these results indicate that PGT ameliorates renal fibrosis in this rat model of diabetes and metabolic syndrome, and suggest that similar effects may occur in the human.