

# GONADECTOMY PREVENTS THE INCREASE IN BLOOD PRESSURE AND GLOMERULAR INJURY IN ACE2 KNOCKOUT DIABETIC MALE MICE

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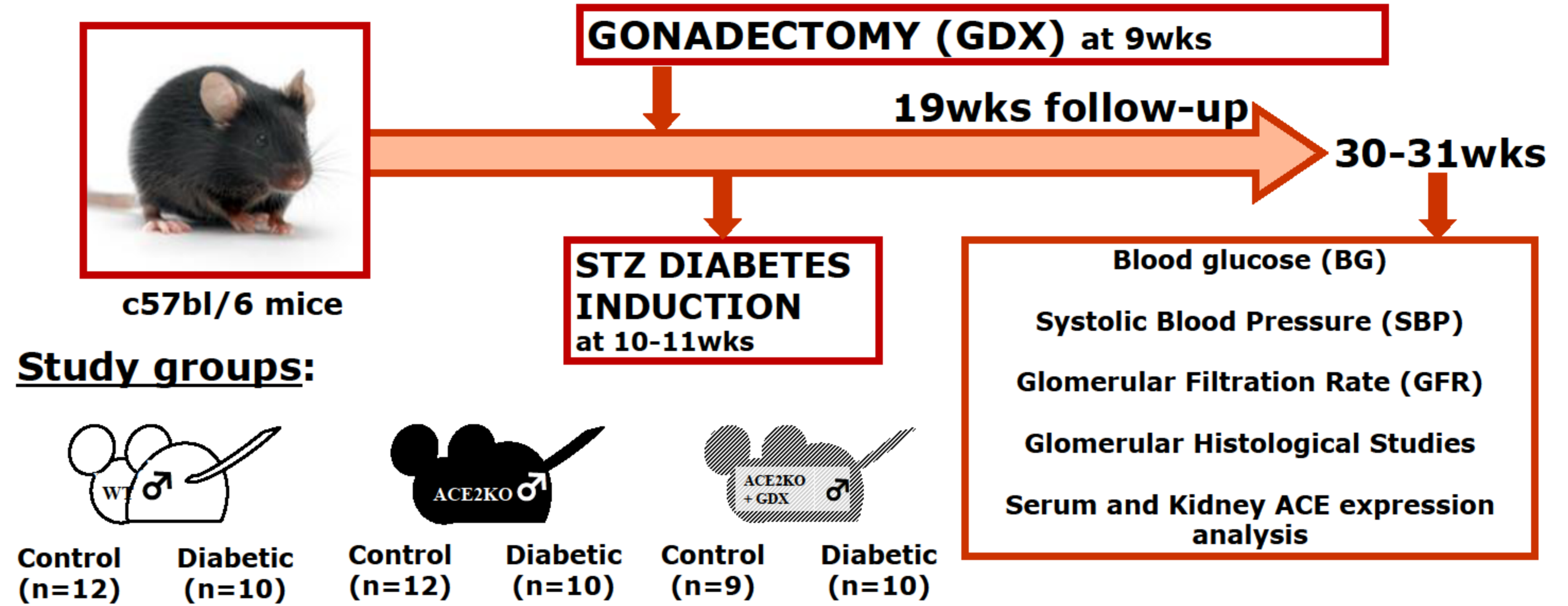
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## INTRODUCTION & AIM

- Whereas ACE2 deletion or inhibition worsens kidney injury<sup>1,2</sup>, its amplification ameliorates diabetic nephropathy<sup>3</sup>.
- We previously showed that circulating ACE2 activity is increased in male diabetic mice<sup>4</sup>.
- The effect of gonadectomy in diabetic ACE2 knockout (ace2KO) male mice has not been previously studied.

## METHODS

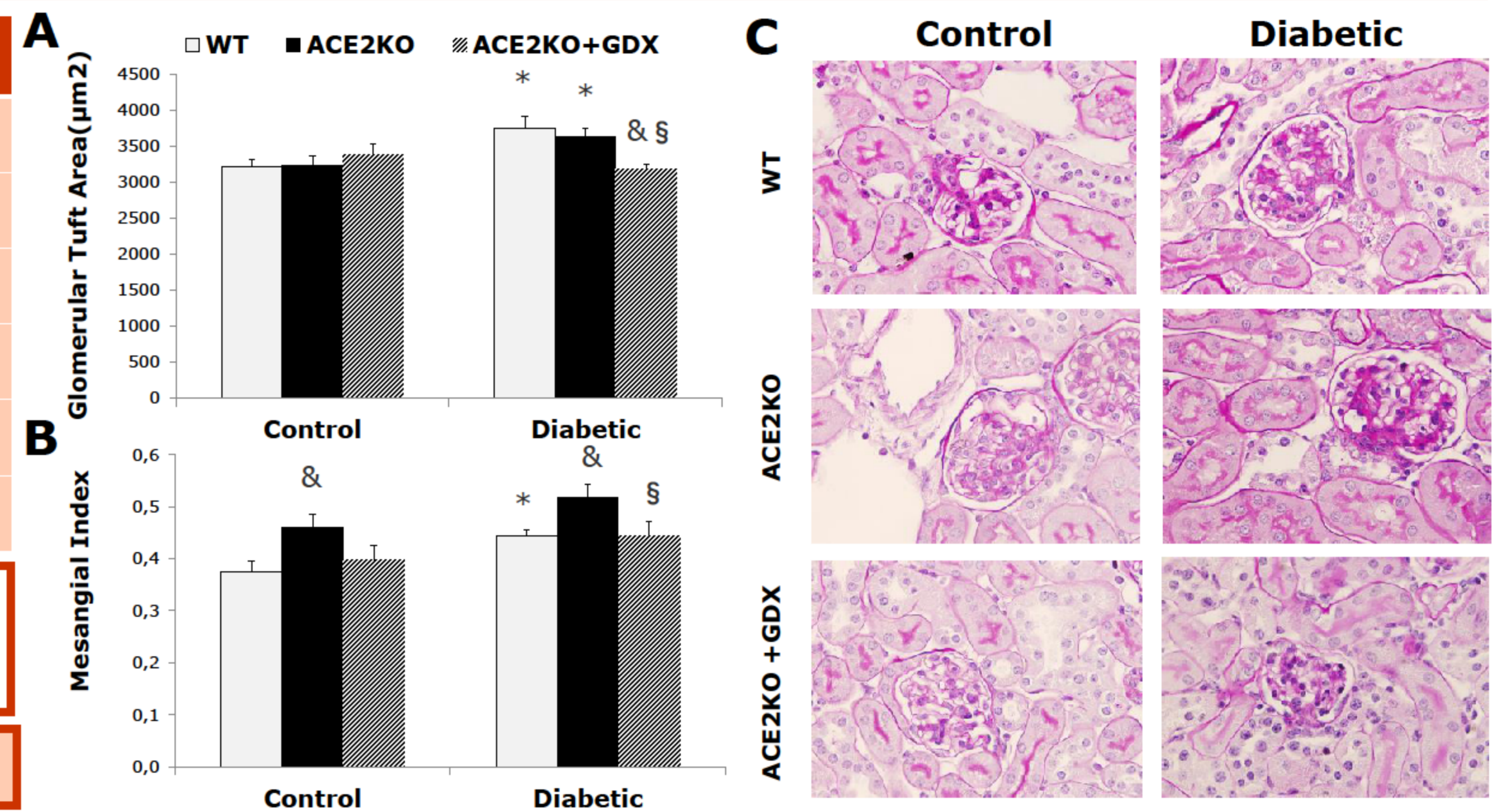


## RESULTS

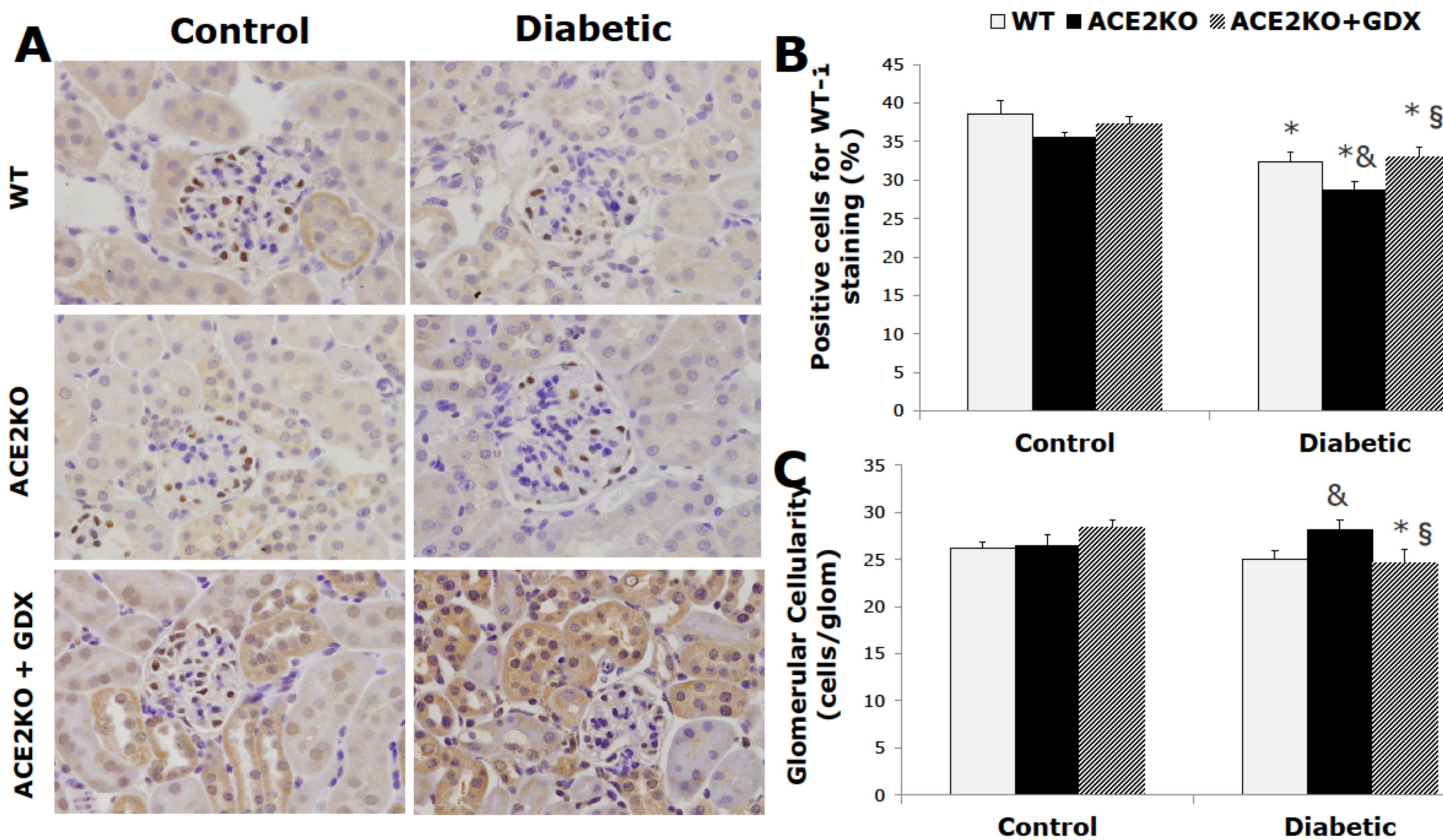
	BG (mg/dl)	SBP (mmHg)	GFR (μL/min/grBW)
WT-CONT	204.7±4.7	96.4±1.3	18.4±2.2
ACE2KO-CONT	194.0±6.7	96.4±1.7	25.3±3.1&
ACE2KO-CONT + GDX	208.5±10.0	100.7±1.4	22.5±1.8
WT-DB	538.3±25.3*	97.5±1.7	28.9±2.8*
ACE2KO-DB	545.6±22.2*	104.4±1.8*&	34.9±5.2*
ACE2KO-DB + GDX	242.1±10.1*&§	95.4±0.5*§	22.9±4.6§

**Table 1. Animal characteristics at the end of the study.** Hyperglycemia was observed in all groups given STZ. ACE2KO diabetic mice had increased SBP and GFR as compared to WT-DB. Gonadectomy significantly reduced BG, SBP and GFR in ACE2KO diabetic mice.

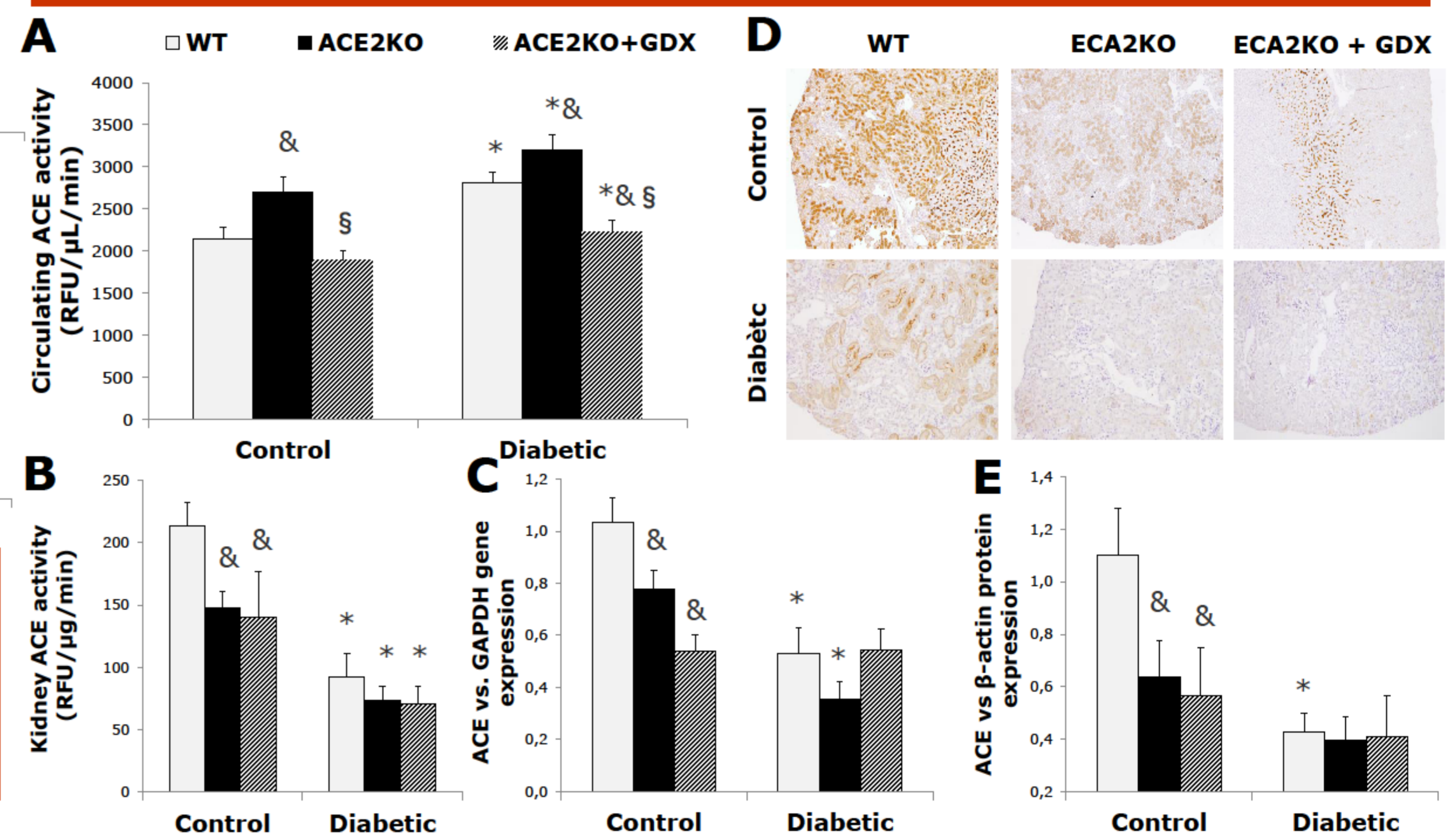
\* p<0.05 vs. CONT; & p<0.05 vs. WT; § p<0.05 vs. non-GDX



**Figure 1. Effect of diabetes, ACE2 deletion and gonadectomy on glomerular structural alterations.** Periodic Acid Staining (PAS) was performed on 3μm kidney sections from all experimental groups. (A) Glomerular tuft area (GTA) and (B) mesangial index (MI) were calculated by ImageJ software. Representative PAS sections from all the experimental groups are shown in panel C. Diabetic WT and ACE2KO mice showed increased GTA and MI as compared to controls. ACE2KO-DB mice had higher MI than WT-DB. Gonadectomy significantly decreased both parameters in ACE2KO diabetic mice.



**Figure 2. Representative photomicrographs depicting glomerular WT-1 staining (A), podocyte number (B) and glomerular cellularity (C) in the studied groups.** Podocyte number is represented as the % of WT-1 stained cells within the glomeruli. Podocyte number was decreased in all diabetic groups as compared to controls. ACE2KO-DB mice had significantly decreased podocyte number and increased glomerular cellularity as compared to WT-DB. Gonadectomy prevented these alterations in ACE2KO-DB.



**Figure 3. ACE expression in serum and kidney.** Circulating ACE was increased in WT and ACE2KO diabetic mice (A). GDX decreased serum ACE in both CONT and DB ACEKO mice. Kidney ACE was reduced by diabetes in terms of enzymatic activity (B), gene (C) and protein (D,E) expression. Renal ACE was also decreased in ACE2KO-CONT mice as compared to WT-CONT. Renal ACE activity positively correlated with gene (F) and protein (G) expression.

## CONCLUSIONS

- Diabetic ACE2KO showed increased blood pressure and glomerular injury as compared to diabetic WT mice. These alterations were prevented by gonadectomy.
- Diabetes and ace2 deletion increased circulating ACE but decreased renal ACE expression.
- Thus, the alterations observed in this model of diabetes may be related to a modulation of ACE at serum and kidney level. This regulation may be mediated, at least in part, by AngII accumulation.

## REFERENCES

1. Soler MJ, Wysocki J et al. ACE2 inhibition worsens glomerular injury in association with increased ACE expression in streptozotocin-induced diabetic mice. *Kidney Int.* 2007;72:614-23.
2. Shiota A, Yamamoto K et al. Loss of ACE2 accelerates time-dependent glomerular and tubulointerstitial damage in streptozotocin-induced diabetic mice. *Hypertens Res.* 2010;33:298-307.
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4. Clotet S, Soler MJ, Rebull M, Pascual J, Riera M. Effect of gender and diabetes in circulating ACE and ACE2 activities in streptozotocin-induced mice. *ASN Kidney Week.* Atlanta 2013.

