EFFECT OF ACE2 DELETION ON RENAL FUNCTION AND STRUCTURE IN NON-OBESE DIABETIC (NOD) MICE

Roca-Ho H[1], Palau V[1], Riera M[1], Rebull M[1], Gimeno J[2], Pascual J[1], Soler MJ[1]

[1]Department of Nephrology, Hospital del Mar-Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain.
[2]Department of Pathology, Hospital del Mar-Institut Hospital del Mar d'Investigacions Mèdiques, Barcelona, Spain.

INTRODUCTION AND AIMS

- ACE2 is altered in diabetic nephropathy (DN)[1,2]. Downregulation of ACE2 either by gene deletion or by pharmacological inhibition worsens DN in STZ and Akita model of type 1 diabetes [3,4,5].
- We hypothesize that loss of ACE2 contributes to an increase in DN progression in the non-obese diabetic (NOD-ACE2$^{-/-}$) mice as compared to non-obese resistant mice (NOR-ACE2$^{-/-}$).

METHODS

- Urinary albumin excretion (UAE) and glomerular filtration rate (GFR) by ELISA kit and inulin-FITC bolus, respectively.
- Systolic blood pressure (SBP), Glomerular hypertrophy, mesangial matrix expansion, podocyte (POD) loss and renal cortex protein expression.
- ACE enzymatic activity in serum and renal cortex was evaluated using a fluorimetric assay.

RESULTS

	GFR (µL/min)	UAE (µg albumin/mg creatinine)	SBP (mmHg)	Renal Cortex Protein Expression (ECA/β-actin)
NOR-ACE2$^{+/+}$	29,4±4,1	17,6±4,0	109,4±2,7	0,8±0,1
NOR-ACE2$^{-/-}$	29,3±5,1	19,9±3,7	104,2±2,4	1,0±0,1
NOD-ACE2$^{+/+}$	54,2±8,3*	770,1±270,2*	117,4±2,4*	0,7±0,1
NOD-ACE2$^{-/-}$	36,3±6,4	512,0±288,3*	117,1±3,3*	0,9±0,1

Table 1. Renal function, blood pressure and protein expression. The table illustrates the values of glomerular filtration rate, urinary albumin excretion and renal protein expression of diabetic and non-diabetic mice WT and KO. NOD mice showed higher UAE and SBP than NOR mice. The GFR was also higher in NOD-ACE2$^{+/+}$ in comparison with NOR-ACE2$^{+/+}$.
*p≤0,05 NOD vs NOR

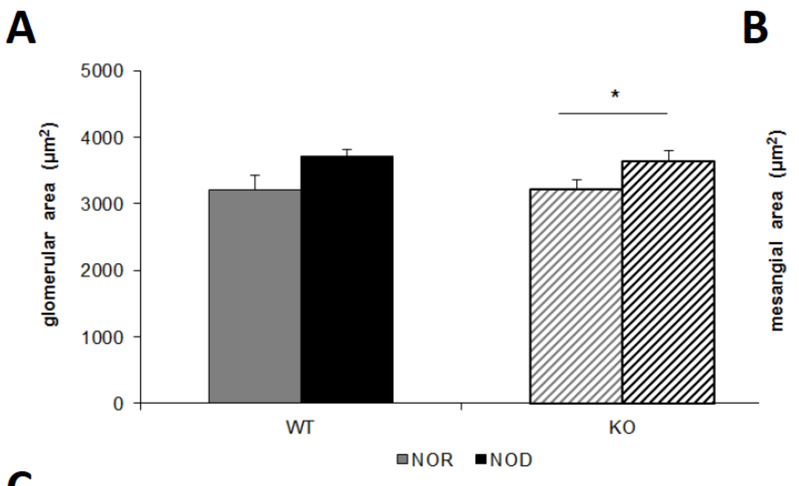

Figure 1. Renal Histology. Glomerular area (A), mesangial area (B) and podocyte number/glomeruli (C) were measured using Image J software. Glomerular and mesangial area was found increased in NODACE2$^{-/-}$ mice as compared to NOR-ACE2$^{-/-}$. Mesangial area was also increased in NOD-ACE2$^{+/+}$ mice in comparison with NOR-ACE2$^{+/+}$. NOD-ACE2$^{-/-}$ mice showed less number of podocytes/glomeruli than NOR-ACE$^{-/-}$ mice.
*p≤0,05 NOD vs NOR

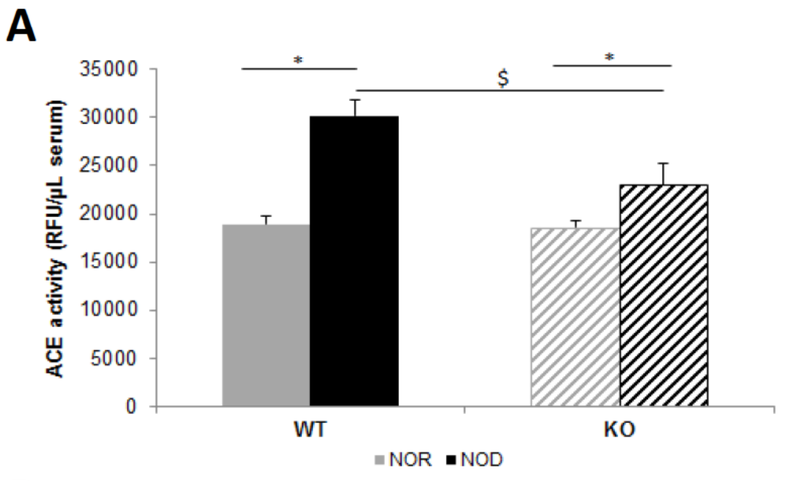

Figure 2. ACE enzimatic activity. ACE activity in serum (A) and renal cortex (B) was measured by a fluorimetric assay. Serum of diabetic mice showed significant increase in ACE activity as compared to non-diabetic mice. NOD-ACE2$^{-/-}$ showed less serum ACE activity than NOD-ACE2$^{+/+}$. NOR-ACE$^{-/-}$ mice showed significant increase in ACE activity in the renal cortex as compared to NOR-ACE2$^{+/+}$.
*p≤0,05 NOD vs NOR; $p≤0,05 KO vs WT

CONCLUSIONS

- The NOD-ACE2$^{-/-}$ mice present an increased diabetic nephropathy progression in terms of increased glomerular area, mesangial matrix expansion and podocyte loss. These alterations are not accompanied by GFR changes in NOD-ACE2$^{-/-}$ mice despite an increase in GFR in NOD-ACE2$^{+/+}$ mice.
- These results demonstrated that ACE2 deletion worsens kidney disease coupled by serum ACE2 in NOD diabetic mice.

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