URINARY EXCRETION OF ANGIOGENESIS FACTORS IN CHRONIC GLOMERULONEPHRITIS PATIENTS: ASSOCIATION WITH CLINICAL ACTIVITY AND URINARY BIOMARKERS OF KIDNEY INJURY

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INTRODUCTION AND AIMS

According to experimental and morphological studies many of angiogenic and angiostatic molecular factors can be produced by renal podocytes and tubular cells regulating reparation of glomerular and peritubular capillaries in chronic kidney disease. The role of disbalance of the angiogenesis regulating factors in development of tubulointerstitial chronic hypoxic injury and fibrosis is discussed.

The aim of the present study was to estimate the urinary excretion of vascular endothelial growth factor type A (VEGF-A), thrombospondin 1 (THBS1), and angiopoietin 2 (ANGPT2) in chronic glomerulonephritis (CGN) patients and to test its possible correlations with CGN clinical activity, renal function and urinary biomarkers of kidney injury and fibrogenesis, such as neutrophil gelatinase-associated lipocalin (NGAL), and type IV collagen (COL4).

METHODS

82 CGN patients (45% men, 55% women; mean age 36.5 (28.0; 55.0)) were examined. Mesangioproliferative GN was revealed in 23.5%, mesangiocapillary GN - in 17.7%, minimal change disease (MCD) - in 14.7%, focal segmental glomerular sclerosis (FSGS) - in 8.8%), membranous nephropathy (MN) - in 23.5%, diffuse nephrosclerosis - in 11.8% (Fig. 1). Nephrotic syndrome was revealed in 31.7%; glomerular filtration rate estimated using the CKD-EPI formula (eGFR) < 60 ml/min/1.73 m^2 was found in 31.7% of the study patients.

Morning urine samples were analyzed by ELISA to determine the excretion of biomarkers (VEGF-A, THBS1, ANGPT2, NGAL, and COL4). The results were adjusted to urinary creatinine concentrations.

RESULTS

The urinary excretion of proangiogenic factor VEGF-A, so as excretion of angiogenesis inhibitors THBS1 and ANGPT2 were strongly correlated with the level of proteinuria (Table 1). In nephrotic syndrome patients the frequency of high (> 75th percentile) urinary excretion rates of all studied angiogenesis regulators were significantly higher: 46.2 and 14.8% for VEGF-A ($p < 0.01$); 50,0 and 13,0% for THBS1 ($p < 0.001$); and 46.2 and 14.8% for ANGPT2 ($p < 0.01$), respectively (Fig. 2). VEGF-A, THBS1, and ANGPT2 urinary excretion correlated with urinary level of NGAL, COL4 and was unassociated with blood pressure, GFR, and degree of nephrosclerosis.

Urinary VEGF-A excretion was significantly higher in patients with “podocytopathic” forms of CGN (FSGS, MCD, MN) compared with mesangial forms (43.8% vs 7.1%, respectively; $p < 0.05$), although the proteinuria level was similar in both groups (Fig. 3). Urinary ANGPT2 excretion was significantly higher in patients with anemia (63.2 versus 11.7%; $p < 0.001$).

CONCLUSION

We did not find renal VEGF depletion associated with renal dysfunction and nephrosclerosis described in other studies. In our study urinary excretion of VEGF, THBS1, ANGPT2 strongly correlates with proteinuria, which is the main marker of glomerular injury and the factor for tubulointerstitial remodeling.

The revealed in our study association of angiogenesis regulators excretion with proteinuria, so as with urinary NGAL and COL4, as biomarkers of kidney injury and fibrosis, gives us an opportunity to consider VEGF, THBS1, and ANGPT2 as participants of renal inflammation and markers of CGN activity.

Fig. 1. CGN morphology in the study patients

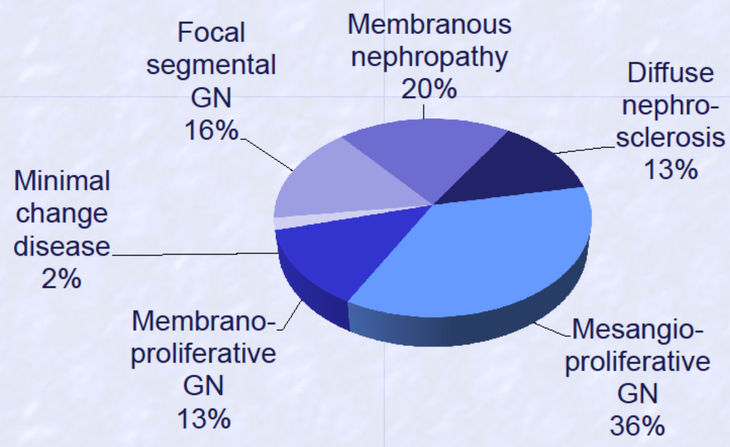

Fig. 2. Association of high (> 75th percentile) angiogenesis factors urinary excretion with nephrotic syndrome (NS)

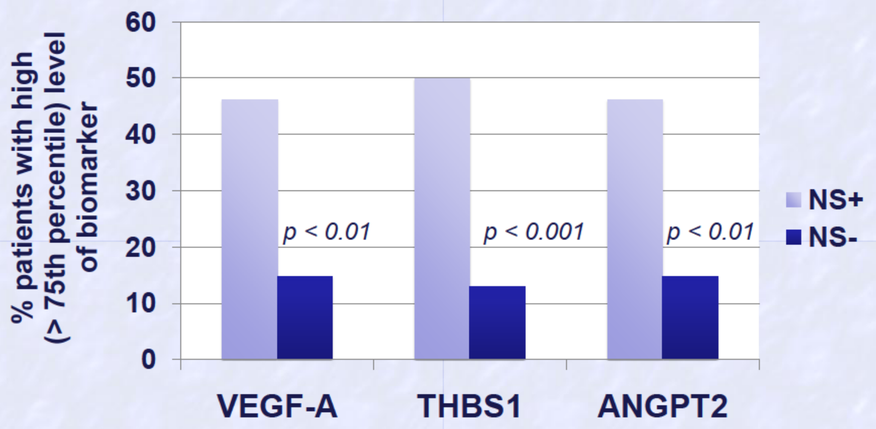

Fig. 3. Association of high (> 75th percentile) VEGF-A urinary excretion with CGN morphology

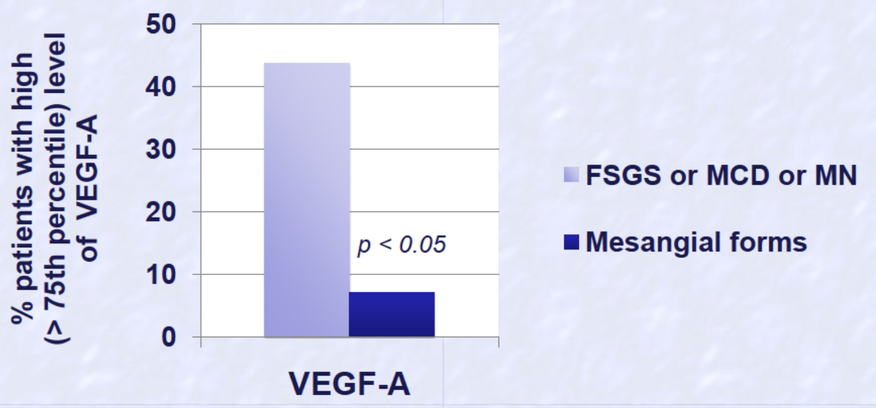

Table 1. Correlation of angiogenesis factors urinary excretion with clinical data and urinary excretion of kidney injury biomarkers in CGN patients

	VEGF-A	THBS1	ANGPT2
Age	Rs = 0,1	Rs = -0,07	Rs = 0,04
CKD duration	Rs = -0,12	Rs = 0,03	Rs = 0,13
SBP	Rs = 0,12	Rs = 0,11	Rs = 0,12
Number of BP lowering drugs	Rs = 0,11	Rs = 0,07	Rs = 0,23
Proteinuria	Rs = 0,51&	Rs = 0,49&	Rs = 0,35#
eGFR	Rs = 0,05	Rs = 0,15	Rs = -0,08
Cholesterol	Rs = 0,39&	Rs = 0,32#	Rs = 0,31#
Triglycerides	Rs = 0,24*	Rs = 0,25*	Rs = 0,25*
Hb	Rs = -0,22	Rs = -0,15	Rs = -0,38&
Fibrinogen	Rs = 0,5&	Rs = 0,2	Rs = 0,38#
NGAL	Rs = 0,36#	Rs = 0,36#	Rs = 0,54&
COL4	Rs = 0,42&	Rs = 0,1	Rs = 0,49&

** – $p < 0.05$, # – $p < 0.01$, & – $p < 0.001$*

DOI: 10.3252/pso.eu.53era.2016