

Renal parenchymal thickness is both related to vascular endothelial growth factor and intrarenal stiffness in systemic sclerosis

Sirs,

Subclinical renal vasculopathy in systemic sclerosis (SSc) is characterised by abnormal renal resistance indices (RRI) with slow reduction of glomerular filtration rate (GFR) (1). A chronic nephropathy has been also demonstrated with reduction of parenchymal thickness and renal length confirming the progressive loss of functional parenchyma (2). Moreover, angiogenesis appears imbalanced and is related to intrarenal stiffness and GFR (3).

Aim of the study is to evaluate the role of vascular endothelial growth factor (VEGF) in relation to renal parenchymal thickness in scleroderma. The study, according to the Declaration of Helsinki, was approved by local Ethics Committee. All patients met the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative criteria for SSc classification (4). Exclusion criteria were diabetes, hypertension, thrombophilia, smoking, renal disorders not related to SSc and scleroderma renal crisis (SRC). Calcium channel blockers therapy and iloprost infusion were discontinued 72 hours before renal Doppler ultrasound (RDU) examination.

Serum VEGF levels in SSc patients were obtained from commercial ELISA kit (Human VEGF, Quantikine ELISA, R&D Systems, Minneapolis, MN, USA), according to the instructions provided by the manufacturer. RDU with evaluation of RRI and parenchymal thickness were measured in according to previously studies (1, 2). Estimated GFR (eGFR) was calculated with CKD-EPI equation (5).

All the results are expressed as mean and SD. Multiple regression analysis was used to evaluate the correlation of clinical variables, intrarenal stiffness and angiogenesis with parenchymal thickness. Group comparisons were made through t-Student's test. Pearson correlation coefficients (r) was used. p -values <0.05 were considered significant. Eighty-seven SSc patients (76 females, mean age 54 ± 13) were enrolled. Forty-five patients have diffuse cutaneous SSc, forty-two have limited cutaneous SSc. Mean duration of disease is 11.8 ± 8.4 years. Mean value of eGFR is 93 ± 21 mL/min, mean parenchymal thickness value is 16.24 ± 2.43 mm, mean RRI is 0.702 ± 0.057 , mean VEGF is 283.4 ± 150 pg/mL. In multiple regression analysis, adjusted for age, parenchymal thickness shows a negative correlation with RRI (β coefficient = -0.760 ,

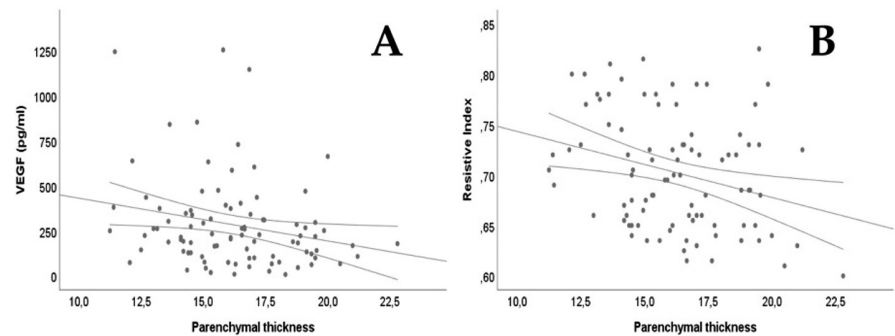


Fig. 1. Correlations between: A) parenchymal thickness and vascular endothelial growth factor (VEGF); B) parenchymal thickness and renal resistive index.

$p < 0.05$) and with VEGF (β coefficient = -0.229 , $p < 0.05$). Figure 1 shows the bivariate correlation of parenchymal thickness with both RRI and VEGF.

The present study reveals the presence of a link between functional parenchyma and angiogenesis. The subclinical renal vasculopathy in SSc is characterised by vascular damage in small- and medium-sized vessels, probably due to renal Raynaud's phenomenon vasospasm episodes, with consequent hypoxia, vasoconstriction and increase in RRI. Progressive loss of nephrons (2) is suggested by the reduction of parenchymal thickness caused by chronic hypoxia, which subsequently determinates the recruitment of angiogenesis.

VEGF, a pro-angiogenic factor, has a controversial role in SSc organ damage. Chronic hypoxia seems to determinate, especially at early stage, the over-expression of VEGF with loss of its down-regulation (6). The imbalance in VEGF is a key factor in chronic vasculopathy, bringing to the disarrangement of tissue vascular network (7). Conversely, in SRC, which represents an acute renal vasculopathy, VEGF does not predict the risk of onset or worsening of crisis (8). This data suggests that the role of VEGF is expressed in chronic damage, particularly at early stage. In chronic kidney disease (CKD) a dysregulated angiogenesis has been proved. The VEGF over-expression is documented in pre-dialysis CKD patients and is a risk factor for disease progression (9).

SSc nephropathy is subclinical with GFR still in normal range; for this reason VEGF is present despite the reduction of parenchymal thickness. Further studies, with consideration of other angiogenesis factors, are required to confirm this data.

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References

- ROSATO E, GIGANTE A, BARBANO B *et al.*: Intrarenal hemodynamic parameters correlate with glomerular filtration rate and digital microvascular damage in patients with systemic sclerosis. *Semin Arthritis Rheum* 2012; 41: 815-21.
- GIGANTE A, BARBANO B, GASPERINI ML, ZINGARETTI V, CIANCHI R, ROSATO E: Renal parenchymal thickness in scleroderma patients is related to intrarenal haemodynamic parameters and Raynaud's renal phenomenon. *J Rheumatol* 2020; 47: 567-71.
- GIGANTE A, NAVARINI L, MARGIOTTA D *et al.*: Angiogenic and angiostatic factors in renal scleroderma-associated vasculopathy. *Microvasc Res* 2017; 114: 41-5.
- VAN DEN HOOGEN F, KHANNA D, FRANSSEN J *et al.*: Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis Rheum* 2013; 65: 2737-47.
- GIGANTE A, BARBANO B, GRANATA G *et al.*: Evaluation of estimated glomerular filtration rate and clinical variables in systemic sclerosis patients. *Clin Nephrol* 2016; 85: 326-31.
- MATUCCI-CERINIC M, MANETTI M, BRUNI C *et al.*: The "myth" of loss of angiogenesis in systemic sclerosis: a pivotal early pathogenetic process or just a late unavoidable event? *Arthritis Res Ther* 2017; 19: 162.
- FRECH TM, MACHIN DR, MURTAUGH MA *et al.*: Implications of endothelial shear stress on systemic sclerosis vasculopathy and treatment. *Clin Exp Rheumatol* 2018; 36 (Suppl. 113): S175-82.
- REISETER S, MOLBERG Ø, GUNNARSSON R *et al.*: Associations between circulating endostatin levels and vascular organ damage in systemic sclerosis and mixed connective tissue disease: an observational study. *Arthritis Res Ther* 2015; 17: 231.
- ANDERSON CE, HAMM LL, BATUMAN G *et al.*: The association of angiogenic factors and chronic kidney disease. *BMC Nephrol* 2018; 19: 117.