

in SSc as low levels significantly correlate with worse capillaroscopic patterns. Future studies are needed in order to ascertain the usefulness of soluble klotho in predicting the risk of developing DUs or PAH, both of which are due to irreversible changes in the microvascular tree, or monitoring the efficacy of vasodilating therapies.

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Contributions: RT conceived the idea, wrote the protocol, enrolled the patients, collected and statistically analysed the data, reviewed the capillaroscopic images, and wrote the final manuscript; FR, MCD, MA collected the clinical data; SB collected and stored the serum samples; TL and TV made the laboratory analyses; SS and MCD performed the nailfold capillaroscopy and reviewed the images; FA and PS critically reviewed the paper. All of the authors approved the final version of the manuscript.

REFERENCES

1. Yamamoto T, Katayama I. Vascular changes in bleomycin-induced scleroderma. *Int J Rheumatol*. 2011; 2011: 270938.
2. Smith V, Thevissen K, Trombetta AC, et al.; EULAR Study Group on Microcirculation in Rheumatic Diseases. Nailfold capillaroscopy and clinical applications in systemic sclerosis. *Microcirculation*. 2016; 23: 364-72.
3. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. *J Rheumatol*. 2001; 28: 1573-6.
4. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis*. 2013; 72: 1747-55.
5. Yalçinkaya Y, Adın-Çınar S, Artım-Esen B, et al. Capillaroscopic findings and vascular biomarkers in systemic sclerosis: Association of low CD40L levels with late scleroderma pattern. *Microvasc Res*. 2016; 108: 17-21.
6. Yalçinkaya Y, Çınar S, Artım-Esen B, et al. The relationship between vascular biomarkers and disease characteristics in systemic sclerosis: elevated MCP-1 is predominantly associated with fibrotic manifestations. *Clin Exp Rheumatol*. 2016; 34: 110-4.
7. Chora I, Guiducci S, Manetti M, et al. Vascular biomarkers and correlation with peripheral vasculopathy in systemic sclerosis. *Autoimmun Rev*. 2015; 14: 314-22.
8. Ahmadi R, Hajjalilo M, Ghorbanihaghjo A, et al. FGF-23, Klotho and vitamin D levels in scleroderma. *Iran J Public Health*. 2017; 46: 530-6.
9. Hajjalilo M, Noorabadi P, Tahsini Tekantapeh S, Malek Mahdavi A. Endothelin-1, α -Klotho, 25(OH) Vit D levels and severity of disease in scleroderma patients. *Rheumatol Int*. 2017 [Epub ahead of print].
10. Talotta R, Bongiovanni S, Letizia T, et al. Measurement of serum klotho in systemic sclerosis. *Dis Markers*. 2017; 2017: 9545930.
11. Geirsson AJ, Wollheim FA, Akesson A. Disease severity of 100 patients with systemic sclerosis over a period of 14 years: using a modified Medsger scale. *Ann Rheum Dis*. 2001; 60: 1117-22.
12. Andrade LE, Gabriel Júnior A, Assad RL, et al. Panoramic nailfold capillaroscopy: a new reading method and normal range. *Semin Arthritis Rheum*. 1990; 20: 21-31.
13. Cutolo M, Sulli A, Pizzorni C, et al. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. *Rheumatol*. 2000; 27: 155-60.
14. Ruaro B, Sulli A, Smith V, et al. Microvascular damage evaluation in systemic sclerosis: the role of nailfold videocapillaroscopy and laser techniques. *Rheumatology*. 2017; 69: 147-55.
15. Morardet L, Audejac J, Sannour M, et al. Late nailfold videocapillaroscopy pattern associated with hand calcinosis and acro-osteolysis in systemic sclerosis. *Arthritis Care Res (Hoboken)*. 2016; 68: 366-73.
16. Piate M, Fatone MC, Favoino E, Perosa F. Raynaud's phenomenon: from molecular pathogenesis to therapy. *Autoimmun Rev*. 2014; 13: 655-67.
17. Cutolo M, Sulli A, Smith V. How to perform and interpret capillaroscopy. *Best Pract Res Clin Rheumatol*. 2013; 27: 237-48.
18. De Santis M, Ceribelli A, Cavaciocchi F, et al. Nailfold videocapillaroscopy and serum VEGF levels in scleroderma are associated with internal organ involvement. *Auto Immun Highlights*. 2016; 7: 5.
19. Bian A, Neyra JA, Zhan M, Hu MC. Klotho, stem cells, and aging. *Clin Interv Aging*. 2015; 10: 1233-43.
20. Lim K, Groen A, Molostvov G, et al. α -Klotho Expression in Human Tissues. *J Clin Endocrinol Metab*. 2015; 100: E1308-18.
21. Kurosu H, Kuro-O M. The Klotho gene family as a regulator of endocrine fibroblast growth factors. *Mol Cell Endocrinol*. 2009; 299: 72-8.
22. Kusaba T, Okigaki M, Matui A, et al. Klotho is associated with VEGF receptor-2 and the transient receptor potential canonical-1 Ca²⁺ channel to maintain endothelial integrity. *Proc Natl Acad Sci U S A*. 2010; 107: 19308-13.
23. Six I, Okazaki H, Gross P, et al. Direct, acute effects of Klotho and FGF23 on vascular smooth muscle and endothelium. *PLoS One*. 2014; 9: e93423.
24. Mazzotta C, Manetti M, Rosa I, et al. Proangiogenic effects of soluble α -Klotho on systemic sclerosis dermal microvascular endothelial cells. *Arthritis Res Ther*. 2017; 19: 27.