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Research Letter

Fibroblast Growth Factor 23 Levels in Pulmonary Involvement Associated With Systemic Sclerosis: A Proof-of-concept Study

To the Editor:

Systemic sclerosis (SSc) is a devastating disease associated with lung involvement, primarily interstitial lung disease (ILD) and pulmonary hypertension (PH).[1] Although computed tomography (CT) and right heart catheterization accurately identify cardiopulmonary injury,[2] their high cost and technical complexity make them inaccessible to most nonspecialized health centers. Thus, the timely detection of lung involvement remains a challenge in real-world settings.

A pathogenic link between autoimmunity, inflammation, and vitamin D imbalance is axiomatic in SSc. Closely associated with vitamin D metabolism is fibroblast growth factor 23 (FGF23), a protein secreted by osteocytes and osteoblasts that plays a role in the bone-kidney axis and calcium-phosphorus balance.[3] A recent study demonstrated that the endothelin-1 (ET-1) receptor, a critical regulator of vascular tone and endothelial proliferation in the lungs, controls the cellular production of FGF23, positioning this molecule as a potential biomarker of clinical relevance.[4]

To assess the feasibility of FGF23 as a marker of lung involvement, we conducted a proof-of-concept study in 29 patients with SSc.[1] Evaluation included skin involvement (modified Rodnan skin score [mRSS]), accumulated organ damage (Medsger Disease Severity Scale [MDSS]), and disease activity (Valentini Disease Activity Index [VDAI]).[5] Exclusion criteria were pregnancy, cancer, infection, parathyroid disease, chronic kidney disease, autoimmune overlap, and use of bisphosphonates or parathyroid hormone analogs. ILD was diagnosed according to the Canadian Scleroderma Research Group decision rule based on clinical evaluation, chest radiography, and pulmonary function tests, and suspected cases were subsequently confirmed by chest CT.[6] For PH, the European Society of Cardiology/European Respiratory Society Guidelines echocardiographic-based definition was used: tricuspid regurgitation velocity > 3.4 m/s plus pulmonary artery systolic pressure > 50 mmHg.[2] Serum levels of FGF23 (Millipore; range 9.9–2400 pg/mL) and 25-hydroxyvitamin D (IBL International) were measured by ELISA. Sera from 23 healthy individuals (22 women) with a median age of 49 (IQR 44–56) years were studied as controls.

This study was approved by the local ethics committee (no. 14-888) and conducted in accordance with the Declaration of Helsinki. All individuals gave their consent to participate.

Of the 29 patients included, 13 had pulmonary involvement: 4 had isolated ILD (100% with diffuse cutaneous SSc [dcSSc]), 5 isolated PH (100% with limited cutaneous SSc), and 4 concurrent ILD and PH (75% with dcSSc). Table 1 summarizes the

Table 1. Data of patients with SSc according to the presence of pulmonary disease.

	Pulmonary Disease, n = 13	No Pulmonary Disease, n = 16	*P*
Age, yrs	50 (44–62)	53 (42–63)	0.82
Women, n (%)	13 (100)	15 (93)	> 0.99
Disease duration, yrs	8 (3–10)	5 (2–8)	0.48
Systemic hypertension, n (%)	5 (38)	1 (6)	0.06
Diabetes mellitus, n (%)	3 (23)	1 (6)	0.30
Sjögren syndrome, n (%)	4 (30)	1 (6)	0.14
Cutaneous involvement, n (%)			0.06
dcSSc	7 (54)	3 (18)	
lcSSc	6 (46)	13 (82)	
Drug therapies, n (%)			
Mycophenolate mofetil	8 (62)	2 (13)	**0.02**
Methotrexate	3 (23)	4 (25)	> 0.99
Calcium channel blockers	8 (62)	5 (31)	0.14
PDE5 inhibitors	3 (23)	0	0.08
ET-1 receptor inhibitors	2 (15)	0	0.19
Pulmonary involvement, n (%)			
Pulmonary hypertension	5 (38)	–	
Interstitial lung disease	4 (31)	–	
Both	4 (31)	–	
Raynaud phenomenon, n (%)	10 (77)	11 (69)	0.70
Modified Rodnan skin score	17 (12–21)	10 (7–14)	**0.02**
Valentini Disease Activity Index	3 (1–3.5)	0.5 (0–1.2)	**0.002**
Medsger Disease Severity Scale	6 (6–8)	2 (1–3)	**< 0.001**
NYHA functional class, n (%)			**0.03**
Class I	9 (69)	16 (100)	
Class ≥ II	4 (31)	0	
Autoantibodies, n (%)			
ANA+	13 (100)	16 (100)	> 0.99
CENP-B+	5 (38)	11 (68)	0.14
Scl-70+	3 (23)	0	0.08
CRP, mg/L	3.1 (1.2–6.8)	2.0 (0.9–3.4)	0.33
ESR, mm/h	30 (18–38)	10 (4–16)	**0.02**
25(OH)D, n (%)			0.21
Normal (≥ 30 ng/mL)	0	2 (13)	
Insufficient (≥ 20 to < 30 ng/mL)	3 (23)	1 (6)	
Deficient (< 20 ng/mL)	10 (77)	13 (81)	
Echocardiographic findings			
LVEF, %	64 (60–66)	64 (60–65)	0.78
PASP, mmHg	35 (3–68)	29 (25–36)	**0.02**
TAPSE, mm	22 (14–25)	22 (20–23)	0.71

Data are presented as median (IQR) unless otherwise specified. Discrete variables were evaluated using the chi-square or Fisher exact test, as appropriate; continuous variables were evaluated using the Mann-Whitney *U* test. Significant *P* values are in bold. 25(OH)D: 25-hydroxyvitamin D; ANA: antinuclear antibody; CENP-B: centromere protein B; CRP: C-reactive protein; dcSSc: diffuse cutaneous SSc; ESR: erythrocyte sedimentation rate; ET-1: endothelin-1; lcSSc: limited cutaneous SSc; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure; PDE5: phosphodiesterase-5; SSc: systemic sclerosis; TAPSE: tricuspid annular plane systolic excursion.

main data. Patients with pulmonary involvement had greater skin damage, disease activity, accumulated organ damage, and deterioration in their functional class. More frequent use of mycophenolate mofetil was observed. A high frequency of vitamin D deficiency or insufficiency was found.

Serum FGF23 levels were higher in patients with SSc than in controls (median 16.3, IQR 9.9–104.5 vs 9.9; 9.9–11.1 pg/mL; $P = 0.01$), for an area under the receiver-operating characteristic curve (AUC) of 0.68 (95% CI 0.54–0.83; $P = 0.02$). Patients with lung involvement had higher FGF23 levels (Figure 1A) than their unaffected counterparts (median 63.0, IQR 11.1–130.4 vs 9.9; 9.9–59.1 pg/mL; $P = 0.02$). No differences were found according to the type of lung involvement. Although FGF23 levels were not correlated with mRSS ($\rho = -0.10$; $P = 0.60$), MDSS ($\rho = 0.24$; $P = 0.20$), or VDAI ($\rho = 0.08$; $P = 0.66$) scores, the discriminative ability of FGF23 to detect pulmonary involvement showed an AUC of 0.74 (0.56–0.93; $P = 0.03$; Figure 1B), with optimal cutoff of 10.5 pg/mL (Youden index). At this value, FGF23 levels showed 84.6% (95% CI 53.6–97.2) sensitivity, 62.5% (95% CI 35.8–83.7) specificity, 2.2 (95% CI 1.1–4.4) positive likelihood ratio, and 0.2 (95% CI 0–0.9) negative likelihood ratio to identify patients with pulmonary involvement.

The role of FGF23 as a component of bone metabolism has been described in SSc. FGF23 levels are linearly associated with the risk of fracture and the presence of calcinosis.[7] Conversely, the role of FGF23 as a disease marker in SSc has hardly been assessed. One study failed to demonstrate the association between FGF23 and skin involvement or disease activity.[3] We also did not observe an association between FGF23 and disease severity, although we did find differences in FGF23 levels between patients with SSc and controls. Be that as it may, the most important and novel finding of our study was that FGF23 levels reliably discriminate patients with SSc who have ILD or PH from their unaffected counterparts. This association has biological plausibility considering that FGF23 levels are elevated in idiopathic pulmonary fibrosis and other inflammatory lung conditions. Similar findings have been replicated in animal models for inflammatory airway disease, whereas exposure of airway epithelial cells to cigarette smoke and FGF23 were found to lead to a significant increase in interleukin-1β release, a prototypical inflammatory and angiogenic cytokine.[8,9] Regarding the PH pathogenesis, a novel metabolic theory postulates a deleterious effect of impaired glucose and lipid processing, oxidative stress, and vitamin D abnormalities in the pulmonary vasculature. In addition to its association with ET-1, FGF23 induces cardiomyocyte hypertrophy through nuclear factor of activated T cell signaling while decreasing nitric oxide availability and increasing oxidative stress, leading to endothelial and vascular smooth muscle cell dysfunction.[4,10]

Pending confirmation through longitudinal studies, this proof-of-concept study paves the way for future diagnostic and therapeutic developments.

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The authors declare no conflicts of interest relevant to this article.

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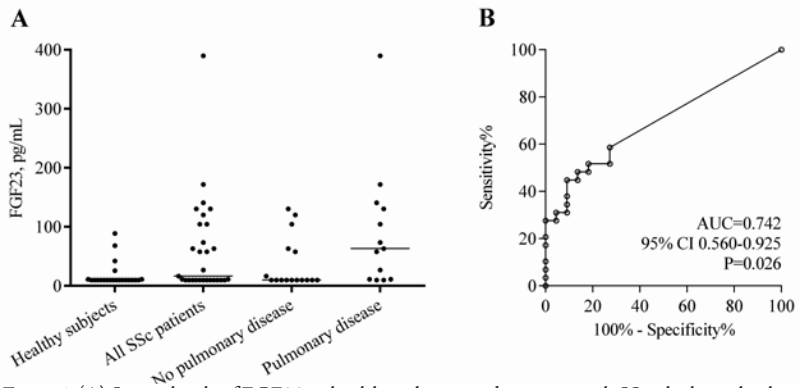

Figure 1. (A) Serum levels of FGF23 in healthy subjects and patients with SSc, the latter both as a group and as a function of the presence of pulmonary disease (either interstitial lung disease or pulmonary hypertension). Horizontal lines denote the median value. (B) AUC of FGF23 to discriminate the presence of pulmonary involvement in patients with SSc. AUC: area under the curve; FGF23: fibroblast growth factor 23; SSc: systemic sclerosis.

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