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Lymphangioleiomyomatosis: circulating levels of FGF23 and pulmonary diffusion

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ABSTRACT

Objective: Lymphangioleiomyomatosis (LAM) is a rare, destructive disease of the lungs with a limited number of determinants of disease activity, which are a critical need for clinical trials. FGF23 has been implicated in several chronic pulmonary diseases. We aimed to determine the association between serum FGF23 levels and pulmonary function in a cohort of patients with LAM. **Methods:** This was a descriptive single-center study in which subjects with LAM and controls with unreported lung disease were recruited. Serum FGF23 levels were measured in all subjects. Clinical data, including pulmonary function testing, were retrospectively obtained from electronic medical records of LAM subjects. Associations between FGF23 levels and clinical features of LAM were explored via nonparametric hypothesis testing. **Results:** The sample comprised 37 subjects with LAM and 16 controls. FGF23 levels were higher in the LAM group than in the control group. In the LAM group, FGF23 levels above the optimal cutoff point distinguished 33% of the subjects who had nondiagnostic VEGF-D levels. Lower FGF23 levels were associated with impaired DL_{CO} ($p = 0.04$), particularly for those with isolated diffusion impairment with no other spirometric abnormalities ($p = 0.04$). **Conclusions:** Our results suggest that FGF23 is associated with pulmonary diffusion abnormalities in LAM patients and elicit novel mechanisms of LAM pathogenesis. FGF23 alone or in combination with other molecules needs to be validated as a biomarker of LAM activity in future clinical research.

Keywords: Lymphangioleiomyomatosis; Fibroblast growth factor-23; Pulmonary diffusing capacity.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare cystic disease of the lungs.[1] It affects almost exclusively young women of childbearing age and occurs sporadically or in association with tuberous sclerosis complex (TSC), the latter of which affects up to 81% of women with the genetic syndrome.[2,3] LAM causes progressive destruction of the lung parenchyma due to accumulation of smooth muscle-like LAM cells that, without cytostatic medical therapy, ultimately results in respiratory failure and death in the absence of lung transplantation.

Loss-of-function mutations in the tumor suppressor genes *TSC1* or *TSC2* result in constitutive activation of the mammalian/mechanistic target of rapamycin pathway, leading to unchecked growth, motility, and survival of LAM cells amongst other abnormalities.[4] LAM cells—in addition to monocytes stimulated by *TSC2*-deficient cells—release VEGF-D,[5,6] which has been validated as a diagnostic biomarker due to its elevation in the peripheral blood of patients with LAM when compared with healthy controls.[6,7] A VEGF-D level greater than 800 pg/mL is 100% specific for LAM but has a false negative rate of about 40%, which, in the absence of other features of LAM (i.e. angiomyolipoma, chylous effusions), often necessitates a lung biopsy.[8] Independent of VEGF-D levels or evidence of pulmonary hypertension, we and others have previously demonstrated that a subgroup of patients with LAM can present with an isolated reduction in DL_{CO}.[9-11]

Abnormal bone mineral density is frequent in patients with LAM and has been associated with estrogen deficiency and pulmonary diseases.[12] FGF23, a thirty-two-kDa protein secreted by osteocytes, is essential for maintaining serum phosphate homeostasis and is dysregulated in human diseases affecting bone mineral density.[13] Accordingly, FGF23 levels positively correlate with airway inflammation in COPD and are elevated in the lungs of patients with idiopathic pulmonary fibrosis (IPF), a disease in which FGF23 reportedly has an antifibrotic and anti-inflammatory role.[14,15] We therefore hypothesized that circulating FGF23 levels would be altered in patients with LAM and be associated with impaired lung function.

METHODS

Adult (≥ 18 years of age) women with LAM and healthy, adult female controls were enrolled at Brigham

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and Women's Hospital (Boston, MA, USA) in protocols approved by the Mass General Brigham Institutional Review Board (2008P002027 and 2012P000840). Written informed consent was obtained from all participating subjects. LAM was diagnosed by established criteria.[16] Subjects with a history of smoking or who were receiving mammalian/mechanistic target of rapamycin inhibitors were excluded. Serum samples were collected from each subject via standardized protocols. Data on age and pulmonary function tests (PFTs) were collected retrospectively from medical records. PFTs were performed in a clinical laboratory according to American Thoracic Society standards.[17] FGF23 concentrations were determined by ELISA (R&D Systems, Minneapolis, MN, USA) as per the manufacturer's protocol.

Baseline age was compared between LAM and control groups by Mann-Whitney U test. Diffusion defect was defined as per American Thoracic Society criteria.[18] Isolated reduction in DL_{CO} was defined as FEV_1 and FVC greater than (i.e., normal) and DL_{CO} less than (i.e., abnormal) the fifth percentile of predicted values. A ROC curve was generated to determine if FGF23 levels were effective in identifying women with LAM versus controls. FGF23 levels below the level of detection of the ELISA test (78.1 pg/mL) were excluded, and levels above the level of detection (5,000 pg/mL at a 1:10 dilution) were assigned a value of 50,000 pg/mL for these analyses. Outliers were excluded by the extreme studentized deviate method. The AUC and corresponding 95% CI were calculated by the trapezoidal and Wilson/Brown methods, respectively. The optimal FGF23 values to differentiate between subjects with and without LAM were determined by the Youden index. The association between FGF23 and VEGF-D levels was determined by Spearman's rank correlation. All statistical analyses were carried out using Stata, version 16.1 (College Station, TX, USA).

RESULTS

We recruited 37 subjects with LAM and 16 control subjects for this analysis. Baseline characteristics of LAM subjects are displayed in Table 1. The median age in the LAM (46 years; IQR, 35-56 years) and control (43 years; IQR, 37-51 years) groups did not differ statistically (p = 0.94). Pulmonary function data for control subjects were unavailable; nonetheless, they had no self-reported history of pulmonary disease. The median interval between phlebotomy for assessment of serum FGF23 levels and PFTs was one day (IQR, 0-31 days).

Table 1. Baseline characteristics of subjects with lymphangioleiomyomatosis (N = 37).[a]

Variable	Subjects
Age, years	46 [35-56]
TSC	6 (16)
FEV_1, % predicted	88 [75-98]
FVC, % predicted	98 [90-108]
DL_{CO}, % predicted	73 [57-88]
Isolated reduction in DL_{CO}	7 (19)

TSC: tuberous sclerosis complex. [a]Values expressed as n (%) or median [IQR]. Data missing: DL_{CO} (n = 1).

Subjects with LAM had higher FGF23 levels than did controls (Figure 1A). A ROC curve assessing the efficiency of FGF23 levels in discriminating between LAM and control groups (Figure 1B) produced an AUC of 0.74 (95% CI, 0.60-0.88; p = 0.0059). The optimal cutoff point of 1,349.0 pg/mL estimated from the ROC curve correctly identified all but 2 controls, yielding a specificity of 87.50%, and 22 subjects with LAM, yielding a sensitivity of 59.46% (positive likelihood ratio of 4.76). FGF23 and VEGF-D levels were inversely correlated ($\rho = -0.37$; p = 0.03). The median FGF23 level in LAM subjects with non-diagnostic VEGF-D levels (< 800 pg/mL) was significantly higher (12,843.9 pg/mL; IQR, 3,044.2-32,096.6 pg/mL) than in those with diagnostic VEGF-D levels (1,365.6 pg/mL; IQR, 395.4-1,690.8 pg/mL; p = 0.01). Of the 22 LAM subjects with elevated FGF23 levels, 21 had VEGF-D level results available for analysis, of which 7 (33%) were below the diagnostic threshold of 800 pg/mL. Conversely, of the 27 subjects with elevated VEGF-D levels, 13 (48%) had FGF23 levels below the optimal cutoff point.

Amongst subjects with LAM, a diffusion defect was associated with lower FGF23 levels (Figure 2A). Subjects with an isolated diffusion defect also had lower FGF23 levels when compared with those with normal DL_{CO} or with accompanying PFT abnormalities (Figure 2B). FGF23 levels were not, however, associated with abnormalities in FEV_1 or FVC.

DISCUSSION

FGF23 has been associated with chronic pulmonary diseases such as COPD and IPF.[14,15] Here, we demonstrate that serum FGF23 levels differentiate LAM subjects from controls and are associated with pulmonary diffusion defects. These findings have not been previously reported, suggest underlying mechanistic differences in disease pathogenesis, and propose a potential candidate biomarker for disease activity in LAM, an unmet need in clinical trial design.

FGF23 is a phosphaturic hormone that acts on tissues via FGF receptors and Klotho, the latter of which acts as a co-receptor.[19] Prior studies have implicated FGF23 and Klotho in pulmonary disease. Plasma levels of FGF23 are increased in patients with COPD and have been associated with a frequent exacerbation phenotype.[20] In both Klotho and FGF receptor 4 knockout mouse models, airway inflammation is increased.[14,21] Furthermore, FGF23 levels are upregulated in subjects with IPF, and co-administration of FGF23 and Klotho have reduced fibrotic and inflammatory markers in TGF-β-stimulated fibroblasts.[15] The present study is, to our knowledge, the first to implicate FGF23 in LAM.

Low Klotho levels have been associated with impaired lung function, including low DL_{CO}, in patients with mild

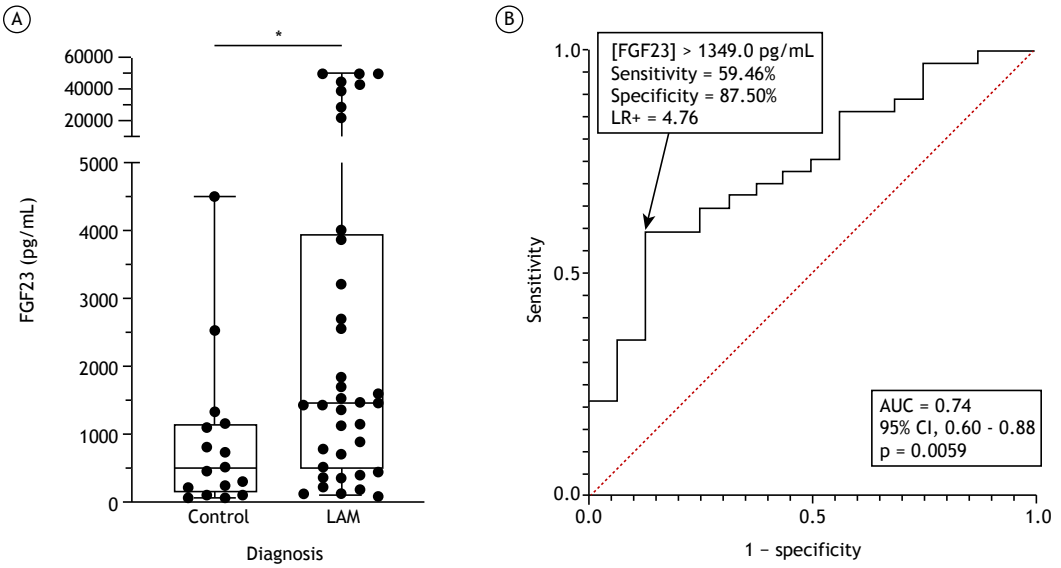

Figure 1. Circulating FGF23 levels differentiate subjects with lymphangioleiomyomatosis (LAM) from healthy controls. In A, serum FGF23 levels in control (N = 16) and LAM (N = 37) subjects. In B, ROC curve assessing the efficiency of serum FGF23 levels in discriminating subjects with LAM from controls. LR+: positive likelihood ratio. *p < 0.05.

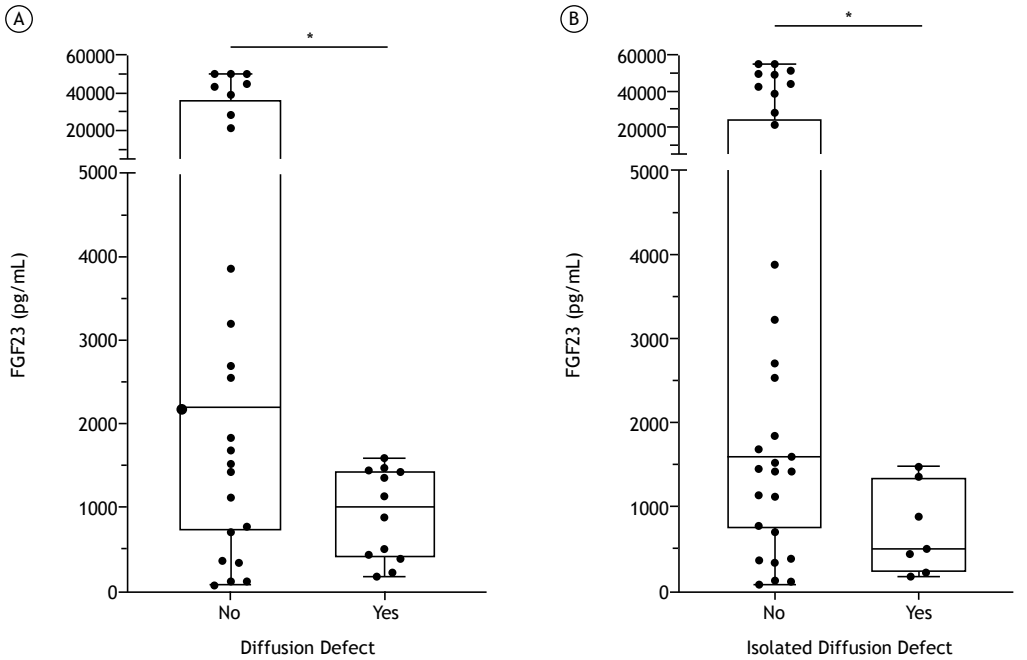

Figure 2. Circulating FGF23 levels are lower in subjects with lymphangioleiomyomatosis (LAM) and pulmonary diffusion abnormalities. In A, serum FGF23 levels in LAM subjects (N = 36) with or without a diffusion defect. In B, serum FGF23 levels in LAM subjects (N = 36) with or without an isolated diffusion defect. *p < 0.05.

nondependent parenchymal abnormalities affecting more than 5% of the lungs on CT scans, which are termed interstitial lung abnormalities.[22] In *TSC2*-deficient cells—such as LAM cells—Klotho has been demonstrated to have a cytocidal effect.[23] Klotho and FGF23 are reciprocally regulated such that patients with low Klotho levels would be expected to have high FGF23 levels.[24] In our study, patients with LAM who had a diffusion defect had lower FGF23 levels, which is distinct from the association described in patients with interstitial lung abnormalities. Given the interplay between FGF23 and Klotho in experimental models and their previously described roles in human respiratory disease, it is tempting to hypothesize that FGF23 not only is a biomarker of LAM but also may contribute to the pathogenesis of the disease. The role of FGF23 in LAM may mirror what has been described for the *MUC5B* promoter variant in IPF—both predicatively

and prognostically.[25,26] Pre-clinical studies examining the role of FGF23 and/or its cofactor Klotho in the pathogenesis and progression of LAM are needed.

Many biomarkers have been described for LAM; however, most do not associate with severity of disease. VEGF-D is a widely used biomarker in the diagnosis of LAM; however, it has a false negative rate of about 40%.[7,8] Our cohort yielded a similar performance, as 8 of the 35 LAM subjects with VEGF-D data available (23%) had levels lower than the diagnostic threshold. Reassuringly, we found that FGF23 correctly identified 7 of these 8 subjects (88%) with LAM and non-diagnostic VEGF-D levels. FGF23 and VEGF-D levels were negatively correlated in our study. A possible explanation for this observation is that FGF23 and VEGF-D may have different regulatory mechanisms and that LAM patients with high FGF23 and low VEGF-D may have a unique clinical phenotype of mild disease. Our data suggest that, once validated, FGF23 may be of diagnostic value in women with "VEGF-D-negative LAM" to obviate the need for lung biopsy.

Identification of biomarkers of LAM disease activity to support clinical trial design is a widely recognized research priority amongst experts in the field.[27-29] Prior research has demonstrated that, in addition to VEGF-D,[30] serum endostatin and vitamin D binding protein levels are correlated with DL_{CO} levels and that the latter is also associated with a progressive disease phenotype.[10,31] Our study suggests that FGF23 may also be a valuable addition to these emerging biomarkers of lung function in LAM patients, as lower levels were associated with a diffusion defect and an isolated reduction in DL_{CO}. Future research is needed to determine the performance of these biomarkers, inclusive of FGF23, potentially as part of a panel that assesses disease activity in LAM patients, which may perform better than any in isolation.

Our study has several important limitations. Although our data identified an association between FGF23, pulmonary diffusion abnormalities, and subjects with LAM, the performance of FGF23 as a potential biomarker of the disease has yet to be verified. We suggest a potential role for FGF23 in the assessment of disease activity; however, future studies will need to validate these findings in an independent cohort to establish generalizability. In addition, our sample size of patients with LAM was small, which is in part due to the extremely low prevalence of the disease. Despite this consideration, we were still able to determine statistically significant associations with important clinical implications, suggesting that the effect size of FGF23 may be substantial. In subsequent studies with larger cohorts, significant power to identify associations between FGF23 and characteristics of patients with LAM will likely boost our conclusions. Furthermore, our study lacks longitudinal assessment. It is possible that FGF23 levels be associated with progressive decline in pulmonary function; for our purposes, such levels were only determined at a single time point. It would be important to determine whether FGF23 levels predict progressive disease, because there would be important therapeutic and prognostic implications.

In summary, we found that serum FGF23 levels were associated with pulmonary diffusion abnormalities and distinguished subjects with LAM from controls. While additional studies are needed to validate our conclusions, these findings may have important implications for future translational research investigations of LAM pathogenesis and for clinical trial design, potentially as a marker of disease activity.

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AUTHOR CONTRIBUTIONS

AJE, AML, MV, HJG, IOR, EPH, and SYE-C: study design. AJE, JI, SS, SB, AML, MV, and SYE-C: data acquisition, analysis, or interpretation. AJE and SYE-C: statistical analysis. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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