

Evaluation of fibroblast growth factor 23 as a marker of severity in stable chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD), a multi-component disease, is one of the leading causes of morbidity and mortality globally. Considering the drawbacks of current severity markers of COPD, there is a need to find newer alternatives that are easily accessible and provide insight into the underlying pathophysiology of the disease. This study evaluated fibroblast growth factor 23 (FGF23), a pro-inflammatory hormone, as a severity marker for COPD. A total of 54 stable COPD patients were recruited as per the inclusion and exclusion criteria. All participants were subjected to spirometry and body plethysmography with diffusion capacity of lungs for carbon monoxide (DLCO) evaluation. Plasma FGF23 levels were measured for all participants. This study aimed to evaluate FGF23 as a severity indicator of COPD, along with its association with serum phosphate levels, static lung volumes, and DLCO. The mean age of the study population (n=54) was 59±11 years. The majority of study participants had moderate COPD (50%), followed by severe (27.8%), mild (20.4%), and very severe (1.9%). The mean plasma FGF23 value observed was 115±169 pg/mL. A significant negative correlation was observed between FGF23 levels and forced expiratory volume in 1 second (FEV1) (% predicted), demonstrating the diagnostic role of FGF23. The phosphaturic action of FGF23 was validated by a strong negative correlation observed between serum phosphate and plasma FGF23 levels. Receiver-operating characteristic curve analysis of FGF23 showed that cut-off levels of 73.71 pg/mL can be used to distinguish mild to moderate COPD from severe to very severe, with a sensitivity and specificity of 62.5% and 68.4%, respectively. FGF23 levels were found to be significantly increased in individuals with poor lung function and compromised lung volumes. FGF23 levels were negatively correlated with FEV1 (% predicted) and can be used as a potential severity marker. Hence, plasma FGF23 levels showed a promising role as a severity marker of COPD.

Key words: COPD, FGF23, spirometry, DLCO.

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Introduction

Chronic obstructive pulmonary disease (COPD) refers to a variety of lung conditions that are characterized by persistent, frequently progressive airflow obstruction caused by abnormalities of the airways and/or alveoli [1]. COPD is one of the leading causes of morbidity and mortality globally, with the highest burden in low- and middle-income countries [2].

COPD is suspected in patients with pertinent clinical symptoms who are subjected to spirometry, in which the presence of a post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio of less than 0.70 confirms the presence of persistent airflow limitation [3]. FEV1 is currently the most commonly used indicator of disease severity and progression of COPD. However, it is not always able to reveal the whole complexity of the illness [4]. It poorly correlates with the clinical presentation of the patient and its symp-

oms. Furthermore, it cannot differentiate among different causes of airflow limitation and does not help in identifying extra pulmonary manifestations of COPD. The decision whether to use the FEV1/FVC ratio or the lower limit of normal and pre- or post-bronchodilator spirometry is challenging. While one parameter might diagnose a patient as COPD, others might not [5]. The existing discrepancy among different parameters and lack of evidence of standardization makes interpretation and diagnosis difficult.

High-resolution computed tomography (HRCT) of the chest can identify the degree of emphysema, but it provides less information in cases of patients with chronic bronchitis. It does not correlate with the clinical severity of the disease. Some patients may exhibit severe emphysema on HRCT chest, while spirometry may grade the disease to be mild and *vice versa*.

In order to fill the existing gap in the diagnosis of COPD, many biomarkers have been identified. Initial studies and research



papers consistently observed hypophosphatemia in patients with COPD. Serum phosphate levels were correlated with degree of respiratory muscle failure and increased morbidity. This further emphasized the need to explore and find the cause for hypophosphatemia in COPD and its role in the pathophysiology of the disease. This brought fibroblast growth factor 23 (FGF23) into the picture.

The hormone FGF23, which is produced from bones and controls phosphate metabolism, is synthesised in response to blood phosphate levels [6]. It is widely known that FGF23 serves as a phosphaturic hormone in the context of chronic renal disease. This circulating pro-inflammatory hormone plays a notable part in augmenting COPD-related inflammation *via* α -klotho, its co-receptor. A detrimental cycle of frequent hospitalization, increased cardiovascular risk, acute worsening, and mortality has been observed in frequent exacerbators of COPD, contributing to persistent systemic and airway inflammation [7].

Current evidence suggests either a direct or an indirect role of FGF23 in the complex pathophysiology of COPD, hence augmenting the need to explore the area and establish a link between the two. However, data on its role as a severity marker is scarce both from India and outside. Considering the drawbacks of currently available markers, there is an urge to identify newer modalities. If an association between FGF23 levels and COPD is established, it would serve as an important severity marker and help optimize treatment. Hence, the current study correlated serum FGF23 levels with existing indicators of severity and lung functions and evaluated its validity to serve as a severity marker for COPD.

Materials and Methods

The study is a cross-sectional study conducted in the Department of Pulmonary, Critical Care, and Sleep Medicine in collaboration with the Department of Biochemistry at Government Medical College and Hospital (GMCH), Chandigarh, over a period of one and a half years from December 2022 to May 2024. 54 patients of stable COPD attending the Pulmonary Medicine Outpatient Department were enrolled in the study. Patients with chronic kidney disease; co-morbidities like obstructive sleep apnoea, interstitial lung disease, lung cancer, and pneumonia; a history of acute cardiovascular event in the preceding 6 weeks; and a history of acute exacerbation of COPD in the preceding 6 weeks were excluded from the study. Informed consent was obtained from all the patients. A detailed clinical history and clinical findings were recorded on a structured proforma at the time of enrollment. Patients having COPD were subjected to spirometry, diffusing capacity of lung for carbon monoxide (DLCO), and body plethysmography for static lung volume measurement. These procedures were performed in the Pulmonary Function Testing Laboratory in the Department of Pulmonary, Critical Care, and Sleep Medicine, GMCH-32, Chandigarh. Spirometry was performed using Helios model no. 702/401, (RMS India, Panchkula, India), for estimation of FVC, FEV1, and FEV1/FVC percentage. Body plethysmography with DLCO was performed using the BODYBOX (Medisoft SA, MGC Diagnostics, Sorinnes, Belgium). The spirometry and body plethysmography were performed in accordance with American Thoracic Society Guidelines Diagnosis of COPD and assessment of severity were done according to the recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1].

Blood samples from each participant were collected under aseptic precautions at the time of recruitment. Apart from routine investigations, a 3 mL blood sample was collected from each participant for measurement of FGF23. The blood sample was allowed to clot. Serum was separated using centrifugation and stored at -20°C. FGF23 levels were then estimated using an ELISA kit. Levels were compared with severity of disease using spirometry and with DLCO and lung volumes. The relationship between FGF23 levels and serum phosphate levels was also evaluated.

Results

The mean age of the study population (n=54) was 59.9±11.6 years. The majority of participants were male (72.2%). Out of 54 participants, 70.4% were ever smokers, with mean pack years of 23.4±14.1 years. Half of the study population (50%) had a history of environmental exposure. Hypertension was the most common co-morbidity encountered, followed by diabetes and old-treatment pulmonary tuberculosis.

The majority of study participants had moderate COPD (50%), followed by severe (27.8%), mild (20.4%), and very severe (1.9%) grades. This grading was done on the basis of post-bronchodilator FEV1 (% predicted) values, as per GOLD guidelines [1]. DLCO<80% was observed in 40.7% of total study participants. Mean FGF23 in participants with DLCO<80% was 165.4±229.2, and in participants with DLCO>80% it was 80.3±103.4. Descriptive analysis of all clinical and pulmonary variables is compiled in Table 1.

Table 1. Data on anthropometrics, pulmonary and clinical variables according to chronic obstructive pulmonary disease status.

Variables	N=54
Age (years)	59.9±11.6 years
Gender (male/female)	39/15
Bmi (Kg/m ²)	25.3±4.3
Smoker (yes/no)	38/16
Pack years	23.4±14.1 years
Hypertension (yes/no)	23/31
Diabetes (yes/no)	13/41
Old treated PTB (yes/no)	11/43
S. Phosphate	2.9±0.67 mg/dL
FGF23 (pg/mL)	115±169 pg/mL
FEV1 (% predicted)	59.7±18%
FVC (% predicted)	73±16.2%
FEV1/FVC	59.2±8.5
Tidal volume	556±70 mL
Inspiratory reserve volume (% predicted)	73.6±11.3
Expiratory reserve volume (% predicted)	68±12.8
Inspiratory capacity	1935±383 mL
Expiratory capacity	1363±284 mL
Vital capacity (% pred)	83.7±13.3
DLCO %	82.2±13.4

Values are mean ± standard deviation or numbers. PTB, pulmonary tuberculosis; FGF23, fibroblast growth factor 23; FEV1, forced expiratory volume in 1 second; FCV, forced vital capacity; DLCO, diffusion capacity of lungs for carbon monoxide.



Table 2. Correlation analyses between fibroblast growth factor 23 and clinical and pulmonary variables in all subjects (n=54).

Variable	Spearman correlation coefficient	p
Age	-0.0	0.896
Body mass index	0.1	0.687
Pack years	-0.1	0.402
S. Phosphate	-0.6	<0.001
FEV1 (% predicted)	-0.3	0.020
FVC (% predicted)	-0.3	0.013
FEV1/FVC	-0.2	0.183
Tidal volume	0.1	0.304
IRV (% predicted)	-0.5	<0.001
ERV (% predicted)	-0.2	0.148
IC	-0.1	0.688
EC	-0.0	0.912
Vital capacity	-0.3	0.012
DLCO %	-0.1	0.354

FEV1, forced expiratory volume in 1 second; FCV, forced vital capacity; IRV, inspiratory reserve volume; ERV, expiratory reserve volume; IC, inspiratory capacity; EC, expiratory capacity; DLCO, diffusion capacity of lungs for carbon monoxide.

Table 3. Correlation analyses between S. phosphate and clinical and pulmonary variables in all subjects (n=54).

Variable	Spearman correlation coefficient	p
Age	-0.0	0.948
Body mass index	0.1	0.344
Pack years	0.2	0.165
FGF23	-0.6	<0.001
FEV1 (% predicted)	0.4	0.006
FVC (% predicted)	0.3	0.009
FEV1/FVC	0.3	0.041
Tidal volume	-0.0	0.909
IRV (% predicted)	0.2	0.128
ERV (% predicted)	0.1	0.286
IC	-0.0	0.953
EC	0.0	0.991
Vital capacity	-0.0	0.956
DLCO %	-0.0	0.973

FGF23, fibroblast growth factor 23; FEV1, forced expiratory volume in 1 second; FCV, forced vital capacity; IRV, inspiratory reserve volume; ERV, expiratory reserve volume; IC, inspiratory capacity; EC, expiratory capacity; DLCO, diffusion capacity of lungs for carbon monoxide.

Table 4. Performance of fibroblast growth factor 23 for predicting chronic obstructive pulmonary disease severity.

Parameter	Value (95% CI)
Cut-off (p-value)	≥73.71 (0.153)
AUROC	0.625 (0.454-0.796)
Sensitivity	62.5% (35-85)
Specificity	68.4% (51-82)
Positive predictive value	45.5% (24-68)
Negative predictive value	81.2% (64-93)
Diagnostic accuracy	66.7% (53-79)
Positive likelihood ratio	1.98 (1.08-3.62)
Negative likelihood ratio	0.55 (0.28-1.07)
Diagnostic odds ratio	3.61 (1.06-12.25)

CI, confidence interval; AUROC, area under the receiver operating characteristic curve.

Correlation analyses between FGF23 and clinical and pulmonary variables are compiled in Table 2. The mean plasma FGF23 value observed was 115±169 pg/mL. A statistically significant negative correlation was observed between FGF23 levels and FEV1 (% predicted), demonstrating the diagnostic role of FGF23 ($p=0.020$, $r=-0.3$). For every 1 unit increase in FEV1 %, the FGF23 (pg/mL) decreased by 1.82 units. There was a moderate negative correlation between FVC % and FGF23 (pg/mL), and this correlation was statistically significant ($p=0.013$, $r=-0.3$).

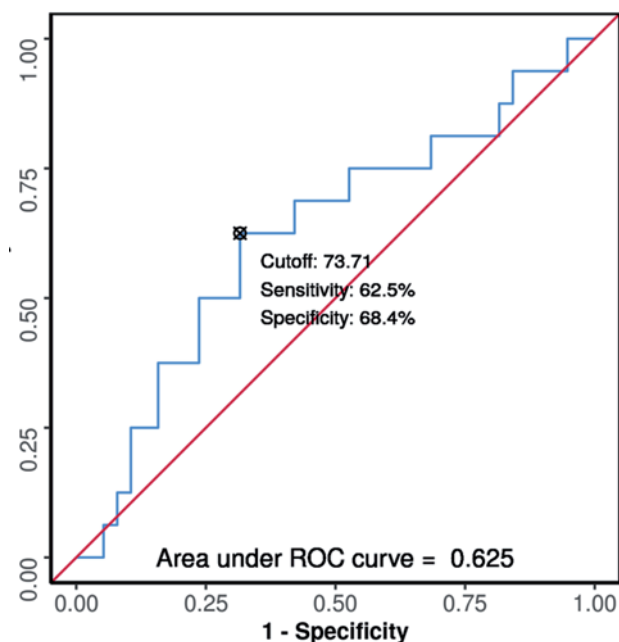
The phosphaturic action of FGF23 was validated by a strong negative correlation observed between serum phosphate and plasma FGF23 levels ($p<0.001$, $r=-0.6$). For every 1 unit increase in S. Phosphate, the FGF23 (pg/mL) decreases by 122.6 units.

Negative correlation between FGF23 with inspiratory reserve volume (% predicted) and vital capacity (% predicted) was also observed. There was no correlation between FGF23 and expiratory reserve volume (% predicted).

No significant relation was seen between FGF23 and DLCO%. Distribution of FGF23 among different severity grades of COPD and GOLD stage was not statistically significant.

Serum phosphate levels were positively correlated with FEV1 % predicted ($p=0.006$, $r=0.4$) and FVC % predicted ($p=0.009$, $r=0.3$). No significant correlation was seen with serum phosphate and static lung volumes (Table 3).

Receiver operating characteristic (ROC) curve analysis of FGF23 showed that cut-off levels of 73.71 pg/mL can be used to distinguish mild to moderate COPD from severe to very severe, with a sensitivity and specificity of 62.5% and 68.4%, respectively (Table 4 and Figure 1).

**Figure 1.** Receiver operating characteristic curve analysis showing diagnostic performance of fibroblast growth factor 2 (pg/mL) in predicting chronic obstructive pulmonary disease severity.

Discussion

This study aimed to evaluate FGF23 as a severity marker in COPD. A total of 54 cases of COPD diagnosed spirometrically (post-bronchodilator FEV1/FVC<70) were enrolled, as per the specified inclusion and exclusion criteria. The mean age of the study population was 59±11 years (range 40-85 years). Out of the total study population, 72.2% were males. This gender distribution is consistent with findings of Aryal *et al.*, which showed that COPD is more prevalent among males as compared to females [8].

Among the 54 participants, 70.4% were ever smokers and 29.6% were non-smokers. Out of smokers, 81.6% of participants were male. Of the 38 participants who were ever smokers, the mean pack years was 23±14 years. Also, the distribution of participants with a history of environmental exposure was equal. 50% of participants with a history of biomass exposure, passive smoking, or occupational exposure were included in this group. Smoking has been attributed as the most important etiology for COPD [9]. Other leading causes among non-smokers include biomass exposure, occupational exposure to dust and smoke, history of pulmonary tuberculosis, poor socio-economic status, and outdoor air pollution [10]. The current study included participants with almost all major etiological factors of COPD to provide more reliable data.

All participants were subjected to spirometry and body plethysmography with DLCO to assess lung functions. Based on the post-bronchodilator FEV1 (% predicted) value, participants were categorized into mild, moderate, severe and very severe, as per GOLD guidelines. The majority belonged to the moderate group (50%), followed by 27.8% in the severe and 20.4% in the mild grade. Only 1.9% of participants belonged to the very severe group. The static lung volumes and DLCO (%) were also assessed. The mean DLCO (%) was 82.2±13.4 %. 40.7% of participants had DLCO<80%. Impaired diffusion capacity in COPD patients is an indicator of underlying emphysema and signifies a meaningful decline in exercise capacity [11].

Plasma FGF23 levels were measured by the commercially available ELISA kit. The mean FGF23 measured was 115±169 pg/mL. The distribution of plasma FGF23 levels among different grades of COPD severity was not significant. The mean FGF23 levels seen in the mild group were 65.75 pg/mL; in the moderate group, 121 pg/mL; in the severe group, 120.8 pg/mL; and in the very severe group, 409.2 pg/mL. This may be attributed to the smaller number of participants included in each group and the fact that all participants included were outpatients and only one had very severe COPD (as per GOLD guidelines) [1]. Also, FGF23 is a pro-inflammatory marker, and its levels may be largely altered by various other factors. It is implicated in the pathophysiology of various other disorders, which are under evaluation. Hence, it is not specific to COPD. Studies suggest that bone and mineral factors, iron status, and erythropoietin levels can affect FGF23 levels, but the role of FGF23 in these is still questionable [12]. To the best of our knowledge, we excluded individuals with chronic renal disease and acute cardiovascular disorders (within 6 weeks) to remove the known confounders [13-17].

The association of plasma FGF23 levels was studied with

spirometry, static lung volumes, and DLCO. The results in the present study showed a statistically significant moderate negative correlation of FGF23 with FEV1 observed, FEV1 % predicted, and FVC % predicted. This signifies that FGF23 levels were found to be higher in individuals with poor lung functions. In the current study, a statistically significant moderately negative correlation of plasma FGF23 levels was established with inspiratory reserve volume (% predicted) and vital capacity (% predicted). Although no statistically significant correlation was found between FGF23 levels and expiratory reserve volume (% predicted). These findings validate the underlying physiological mechanism in obstructive lung diseases. Air trapping in COPD leads to a significant increase in residual volume. This generates a higher positive pressure at the end of expiration. As a result, during inspiration, inspiratory capacity declines. This decline is attributed to a fall in the inspiratory reserve volume, whereas tidal volume remains almost the same. Also, no change in expiratory reserve volume is observed in patients with COPD, as compared to normal individuals [18]. Some studies have also indicated that inspiratory capacity is a better indicator of severity of COPD than FEV1 % predicted [19].

In our study, no statistically significant correlation of plasma FGF23 levels was observed with DLCO (%). This is in contrast to a study, which claims to be the first study to evaluate the association of FGF23 with DLCO [20]. According to them, a clinically significant correlation was established between FGF23 and DLCO %. The reason for such disparity lies in the fact that DLCO % is found to be decreased in the emphysematous phenotype of COPD, while it remains unaffected or within normal limits in the airway-disease-dominant phenotype. HRCT chest is warranted to identify the degree of emphysema and to correlate between the two [21].

Also, a statistically significant strong negative correlation was seen between FGF23 and serum phosphate levels, thus confirming the phosphaturic action of FGF23. For every 1 unit increase in serum phosphate, the FGF23 (pg/mL) was found to decrease by 122.6 units.

Since hypophosphatemia is known to augment respiratory muscle failure, its association with lung functions was also studied [22]. A statistically significant moderate positive correlation of serum phosphate levels was established with FEV1 observed, FEV1 % and FVC % (Table 3). However, no clinically significant correlation was observed between serum phosphate levels and static lung volumes.

ROC curve analysis of FGF23 levels in the current study showed that cut-off levels of ≥73.71 pg/mL can be used to predict COPD severity as severe-very severe with a sensitivity of 62% and a specificity of 68% (Figure 1). Conversely, levels <73.71 pg/mL predict COPD severity as mild-moderate. The area under the ROC curve for FGF23 predicting COPD severity was 0.625, thus demonstrating poor diagnostic performance. The diagnostic accuracy of FGF23 in predicting COPD came out to be 66.7% as per the current study. FGF23 holds a positive predictive value of 45.5% and a negative predictive value of 81.2%. However, the validity of the above results is questionable, owing to the paucity of literature and smaller sample size.

The findings suggest an indirect role of FGF23 in COPD. In



the present study, FGF23 has been demonstrated to be a potential cause of hypophosphatemia in COPD by a statistically significant strong negative correlation between the two. Both plasma FGF23 and serum phosphate levels show statistically significant correlation with spirometrically determined lung functions. These findings imply that FGF23 causes respiratory muscle failure and increases mortality, morbidity, and hence, the severity of COPD through hypophosphatemia. FGF23 is reflected as a cause of hypophosphatemia in COPD. Furthermore, raised FGF23 levels cause serum phosphate levels to fall significantly, thus increasing the severity of the disease. On the other hand, FGF23 is a pro-inflammatory hormone. Its association with inflammation is ancient. Current studies also imply its role in aging. COPD is regarded as an inflammatory lung disorder, with higher prevalence in older age groups. Joining the dots and the findings of our study, we infer that FGF23 is anticipated to play a pivotal role in the pathophysiology of COPD. It can serve as a potential severity marker of the disease, which increases morbidity and mortality indirectly, by decreasing intestinal phosphate absorption, thus causing hypophosphatemia. Although, confirmation of these findings needs more scrutiny. Since this study was one of a kind, and with scarce data available in this area, the results of this study can pave a way for further research in this domain.

The current study had a few limitations. Firstly, inclusion of a smaller number of participants in each grade of severity may have affected the power of the study. Secondly, current literature is deficient in determining the effects of pharmacology on FGF23 levels. It can be hypothesized that oral or inhaled corticosteroids may have a detrimental effect on plasma FGF23 levels, and the same was not evaluated. Also, long-acting β -agonists and long-acting muscarinic agents may also have similar effects. Since all participants were already diagnosed cases of COPD, the ongoing treatment might have influenced the results. Thirdly, a few studies have shown a prognostic role of FGF23 levels in COPD [7]. The current study aimed to evaluate only the diagnostic power of FGF23. Lastly, our study did not include individuals with acute exacerbation. Only stable COPD from outpatients were included.

Conclusions

Research on diagnostic role of FGF23 in COPD is sparse. Plasma FGF23 levels were found to show a promising role as a severity marker of COPD. Phosphaturic action of FGF23 was also validated. FGF23 levels were found to be significantly increased in individuals with poor lung functions and compromised lung volumes. Low serum phosphate levels were also associated with poor lung functions. FGF23 levels were negatively correlated with FEV1 (% predicted) and can be used as a potential severity marker. However, further research and studies using larger sample sizes may help to validate these findings.

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Informed consent: written informed consent for the use of data was obtained from the index cases during the study.

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