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Research Letter

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Periostin Levels do not Distinguish Chronic Obstructive Pulmonary Disease Patients With Frequent and Infrequent Exacerbations

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ABSTRACT

Background: Periostin, an extracellular matrix protein, is involved in inflammatory processes of the lung. To date, most studies have focused on periostin in asthma patients, its role in chronic obstructive pulmonary disease (COPD) is less clear and no information has been reported on blood levels of periostin in COPD patients in the context of exacerbation rates. As such, this exploratory study aimed to investigate whether periostin is helpful to distinguish between COPD patients with frequent and infrequent exacerbations.
Methods: We performed an examination of patients with COPD participating in a COPD cohort study in Switzerland. Periostin levels were determined in serum samples by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. Patients underwent evaluation of clinical symptoms including exacerbation rate (exacerbation defined by requiring oral corticosteroids and/or antibiotics) and lung function. In a subgroup of patients an annual follow-up was available that was considered in an additional analysis.
Results: Twenty six patients (global initiative of obstructive lung disease (GOLD) stage 1 none, 31% stage 2, 38% stage 3, 31% stage 4) were included in the analysis. The mean±standard deviation (SD) age of the patients was 63±5.9 years, 16 were males, 24 were smokers or ex-smokers. The median (quartiles) post-bronchodilator FEV_1% predicted was 36(27/57). There was no significant difference in periostin levels between patients with frequent and infrequent exacerbations. The follow-up data revealed no evidence that periostin is helpful in distinguishing frequent from infrequent exacerbators.
Conclusion: Our analysis performed in a small group of carefully matched COPD patients demonstrates that there is no significant relationship between exacerbation rate and periostin levels in blood.

KEYWORDS: COPD; Periostin; Eosinophilic inflamation; Exacerbations.

ABBREVIATIONS: BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; ELISA: Enzyme-Linked Immunosorbent Assay; FEV_1: Forced expiratory volume in one second; GOLD: Global Initiative of Obstructive Lung Disease; SD: Standard Deviation; WISDOM: Withdrawal of Inhaled Steroids during Optimised bronchodilator Management; QoL: Quality of Life; CGPS: Copenhagen General Population Study.

Trial Registration: https://clinicaltrials.gov/, NCT01527773. Registered 18.01.2012 (retrospectively registered).

To the Editor,

Periostin, a multifunctional matricelluar protein, has been reported to be an excellent predictor of airway eosinophilia.[1] Eosinophilic inflammation within the airways is usually considered as a hallmark of patients with asthma and it was found that the exacerbation rate was significantly reduced in patients with high levels of periostin.[2] While, to date, most studies have focused on

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periostin in asthma, its role in COPD is less clear and no information has been reported on blood levels of periostin in COPD patients in the context of exacerbation rates. However, recent publications focused on the important role of eosinophils and their association with exacerbation rate.[3,4] Moreover, COPD patients with elevated eosinophil counts also had an increased risk of exacerbations.[5] A recent publication implied that high blood eosinophils and high plasma periostin were associated with improved lung function three months after starting treatment with inhaled corticosteroids in combination with a long acting bronchodilator.[5]

These data suggest that periostin may serve as a biomarker in COPD patients. As such, this exploratory study aimed to gain insight whether periostin is helpful to distinguish between COPD patients with frequent and infrequent exacerbations.

We performed an examination of patients with COPD participating in a COPD cohort study from seven pulmonary clinics in Switzerland (NCT01527773). The cantonal ethics committee of Zurich approved the study and patients provided written informed consent (KEK-ZH-Nr. 2011-0106). Periostin levels were determined in serum samples by using a commercially available ELISA kit (Thermo Fisher Scientific, Zug, Switzerland). COPD severity was defined according to GOLD guidelines. Patients underwent evaluation of clinical symptoms including exacerbation rate (exacerbation defined by requiring oral corticosteroids and/or antibiotics) and lung function. All patients were examined in a stable phase of the disease and, in case of an acute exacerbation, the evaluation was postponed by at least 6 weeks.

Comparisons among groups were performed with paired *t*-test, Wilcoxon signed ranks test and chi-square test.

Since the number of patients with frequent exacerbations (≥2 per year) was considerably lower than the number of patients with infrequent exacerbations, we matched every patient from the frequent exacerbator group to a patient with infrequent exacerbations. Matching criteria included age, body mass index (BMI) and disease severity according to FEV_1. Smoking was considered as additional confounder in the analysis because it has been reported recently that periostin may be repressed by smoking.[6]

Twenty six patients (GOLD stage 1 none, 31% stage 2, 38% stage 3, 31% stage 4) were included in the analysis. The mean±SD age of the patients was 63±5.9 years, 16 were males, 24 were smokers or ex-smokers. The median (quartiles) post-bronchodilator FEV_1% predicted was 36(27/57). There was no significant difference among the two groups for demographic data. In a subgroup of patients an annual follow-up was available that was considered in an additional analysis.

When COPD patients with frequent exacerbations were compared to their matched peers with infrequent exacerbations, no signifcant difference in periostin blood levels was detected. Since in a subgroup of patients annual measurements were available, we also analyzed patients that changed their exacerbation frequency over time, e.g. from frequent to infrequent or *vice versa*. This additional analysis provided no evidence to support that periostin is helpful in segregating both groups. No correlation was found between the level of serum eosinophils and periostin in our cohort (Table 1).

Frequent exacerbations, predominantly found in patients with severe COPD, result in accelerated disease progression and mortality.[7] These patients usually have a more rapid decline in lung function, worse quality of life (QoL) and decreased exercise performance. In a stepwise regression performed in more than 2000 COPD patients the history of previous exacerbations was found to be the strongest predictor of subsequent COPD exacerbations.[8]

In addition, a number of previous studies were undertaken to identify biomarkers that may help to predict exacerbation frequency.[9] To date, however, no serum biomarkers reliably predict exacerbation frequency in COPD patients.

Blood eosinophils in COPD have been shown to predict corticosteroid responsiveness during acute exacerbation. Patients with a peripheral blood eosinophil count of ≥2% at the onset of an outpatient managed exacerbation responded promptly to prednisolone, whereas those with a count of <2% had a higher rate of treatment failure compared with placebo.[10] In a post-hoc analysis of the withdrawal of inhaled steroids during optimised bronchodilator management (WISDOM)-trial Watz and colleagues[4] demonstrated that withdrawal of inhaled corticosteroids in COPD patients with an elevated baseline serum eosinophil count led to a higher risk of moderate to severe exacerbations. The authors concluded that an eosinophil count of 4% or greater 300 cells per µl may predispose to a deleterious effect of inhaled corticosteroid withdrawal.[4] A recent analysis of the data from the Copenhagen General Population Study (CGPS) revealed that in COPD patients an increased blood eosinophil level above 0.34 (gram/liter) g/l was associated with a 1.76-fold increased risk of severe exacerbations.[3]

While these publications highlight the role of eosinophils in COPD, in particular in the context of acute exacerbations, to the best of our knowledge our study is the first report on the levels of periostin in COPD and exacerbation rate.

The current analysis focusing on the role of periostinin stable patients with COPD however did not help to stratify patients into frequent or infrequent exacerbators.

Smoking was recently postulated to repress periostin at the individual gene level.[6] However, in our study only 1 patient in the infrequent exacerbation group and two patients of the frequent exacerbators were active smokers and the association

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	All COPD patients (n=26)	Infrequent exacerbators (n=13)	Frequent exacerbators (n=13)	*p* value
Clinical characteristics				
Age, years	63(5.9)	64(6.2)	61(5.6)	0.059
Male/Female	16/10	8/5	8/5	1.000
Body mass index, kg/m^2	25.7(23.5/28.1)	26.6(24.7/28.1)	24.5(22.9/26.5)	0.422
Pack years of smoking	38(26.4)	46(29.6)	29(20.7)	0.148
Current smokers, N(%)	3(12)	1(8)	2(15)	
LAMA+LABA, N(%)	2(8)	2(15)	0(0)	0.157
LAMA+LABA+GC, N(%)	20(77)	10(77)	10(77)	1.000
Lung function				
FEV_1, % pred.	36(27/57)	41(23/57)	33(28/57)	0.779
FVC, % pred.	77(15.7)	78(15.8)	76(16.2)	0.672
TLC, % pred.	115(21.5)	117(21.6)	113(21.9)	0.497
RV/TLC-ratio	138(45.8)	133(55.9)	142(35.1)	0.394
DLCO, % pred.	36(32/47)	36(33/47)	37(32/60)	0.136
Blood gas analysis				
PaO_2, kpa	9.4(8.1/11.0)	8.8(8.1/9.9)	9.5(8.1/11.0)	0.753
$PaCO_2$, kpa	5.0(0.7)	5.2(0.8)	4.8(0.6)	0.113
Laboratory parameters				
Periostin, ng/ml	9.39(6.79/17.93)	7.85(6.40/9.04)	12.32(9.73/20.21)	0.133
Hemoglobin, g/dl	14.6(1.2)	14.6(1.4)	14.6(1.1)	0.865
Leukocytes, G/l	8.6(2.08)	8.1(2.13)	9.1(1.99)	0.215
Lymphocytes, G/l	1.56(1.27/2.12)	1.60(1.46/1.89)	1.42(1.20/2.42)	0.534
Neutrophils, G/l	6.15(1.93)	5.67(1.72)	6.72(2.08)	0.144
Eosinophils, G/l	0.08(0.05/0.16)	0.08(0.08/0.16)	0.08(0.03/0.16)	0.267
CRP, mg/l	2.5(1.1/4.0)	2.6(1.2/4.0)	1.5(1.0/4.0)	0.382

Values are mean(SD) or median(quartiles) unless otherwise stated; LAMA: long-acting muscarinergic antagonist; LABA: long-acting beta-agonist; GC: glucocorticoids;FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; DLCO: Diffusing capacity of the lung for carbon monoxide. *p<0.05 for comparison of differences between the two groups.

Table 1: Characteristics of patients with frequent and infrequent exacerbations.

between smoking status and periostin level was not significant. Moreover, recent findings from a large cross-sectional study suggested that serum levels of periostin do not have to be adjusted for smoking history, age and gender.[11] As such, it is unlikely that the levels of periostin in our cohort have been under estimated.

In summary, our observation, although limited by the small size, suggests that serum periostin levels do not help distinguishing COPD patients with frequent from those with infrequent exacerbations. Future studies will have to determine whether periostin levels are useful in guiding therapeutic strategies in patients with COPD as it has been demonstrated in asthma patients.

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CONFLICTS OF INTEREST

None of the authors has competing interest relating to this article.

CONSENT

The Cantonal Ethics Committee of Zurich approved the study and patients provided written informed consent (KEK-ZH-Nr. 2011-0106). The study was performed in accordance with the Declaration of Helsinki.

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