Utility of Total Desmosine as Biomarker for Chronic Obstructive Pulmonary Disease Patients

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Abstract

Matrix degradation is a key feature of COPD, leading to lung destruction, emphysema and impaired pulmonary function. Desmosine and isodesmosine are elastin-derived cross linked amino acids whose urine levels are considered representative of elastin breakdown. However, there is a lack of biomarkers to measure disease activity and disease progression in COPD.

Aim: This study was done to determine the utility of urine and blood desmosine as a biomarker in diagnosis of COPD patients and to evaluate their relationship with lung function parameters.

Methods: The urine and blood desmosine levels were measured using validated isotope dilution liquid chromatography tandem mass spectrometry methods in 151 subjects including 101 COPD patients and 50 healthy control subjects.

Results: The COPD patients had higher levels of u-desmosine and b-desmosine compared with healthy smokers and non-smokers. There was statistically significant difference in the mean levels of u-desmosine and b-desmosine between the different severity groups of the COPD patients. After adjustments for age, sex, and BMI; the concentrations of u-desmosine and b-desmosine were significantly correlated with FEV1% and DLCO% (p<0.05) among the COPD patients. The elevation of b-desmosine levels above cutoff of 0.30 ng/ml was not specific for COPD and was found in 69% of all COPD patients. This cutoff value had a diagnostic sensitivity of 71% and specificity of 53%.

Conclusions: This study has demonstrated that both u-DES and b-DES levels were significantly elevated among COPD patients. Also, u-DES or b-DES levels are correlated with COPD severity and some lung function parameters.

Keywords: Desmosine; Biomarker; Chronic Obstructive Pulmonary Disease (COPD)

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem. It is the fourth leading cause of chronic morbidity and mortality in the United States, and is projected to rank fifth in 2020 in burden of disease caused worldwide, according to a study published by the World Health Organization [1]. COPD is characterized by a specific pattern of inflammation involving neutrophils, macrophages, and lymphocytes. These cells release inflammatory mediators and enzymes that interact with structural cells in the airways and lung parenchyma leading to destruction of lung parenchyma [2]. Matrix degradation is a key feature of COPD, leading to lung destruction, emphysema and impaired pulmonary function. The elasticity and resilience of the lungs are mainly provided by elastin, which is synthesized as a soluble precursor, tropoelastin [3]. Elastin synthesis involves secretion of tropoelastin, which is a 72-KD monomer, into the extracellular space by elastin-synthesizing cells, then cross-linking of monomers by two amino acids, Desmosine and Isodesmosine (DI) [4]. The cross-linking transforms the soluble tropoelastin precursor to the insoluble cross-linked mature elastic fiber. DI occurs only in mature elastin, and their presence in body fluids is a chemical indicator of degradation of mature elastic fibers [5]. They are released, either in free form or conjugated to peptides, as a result of elastin degradation, and can be found in sputum, blood and urine [6,7]. Classification of COPD is usually based on the severity of airflow obstruction, as assessed using forced expiratory volume in 1 s (FEV1) [1]. However, there is a lack of biomarkers to measure disease activity and disease progression in COPD [8]. Desmosine and isodesmosine have been proposed as biomarkers of lung matrix degradation in COPD [9-11].

Materials and Methods

The current study included 2 groups:

Group 1

It included 101 COPD patients (53 men and 48 women) with a mean age of 61.0 ± 4.60 years This group included 56 patients with stable COPD and 45 patients with COPD with exacerbation seen at the Pulmonology Department of King Fahad Hospital in Dammam, Kingdom of Saudi Arabia. The study was approved by the Ethics and Research Committee. All patients and control subjects gave their written informed consent before participating in the study. The diagnosis of COPD was established by clinical symptoms, physical examination, chest radiography and pulmonary function test according to the guidelines of GOLD 2013. The COPD subjects were classified into (stages I-IV) on the basis of their post-bronchodilator forced expiratory volume in one second (FEV1)/Forced Vital Capacity (FVC) and FEV1 % predicted. FEV1/FVC was<70% and their FEV1 fell into set bands (stage 1: FEV1 ≥ 80%; stage 2:50% ≥ FEV1<80%; stage 3:30% ≥ FEV1<50%; stage 4:FEV1<30%).

Stable chronic obstructive pulmonary disease: Stable COPD is defined by the absence of any exacerbation for 3 months preceding the study [12].

Chronic obstructive pulmonary disease exacerbation: The American Thoracic Society (ATS) and European Respiratory Society

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Measurement of urine and blood desmosine

Sampling: The stable COPD patients had spotted urine and blood samples collected during a checkup at OPD visit. The COPD with exacerbation patients had urine and blood samples collected during hospital admission. Healthy subjects had spotted urine and blood samples. Urine samples were collected and frozen at -80°C until analysis. Similarly blood samples were separated and sera were collected and frozen at -80°C until analysis (Table 2).

Measurements: Urine creatinine concentration was measured for each urine sample using assay kits purchased from Abcam Inc. (330 Cambridge Science Park, Cambridge CB4 0FL, UK) and corrected for hemoglobin and carboxy hemoglobin [14].

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences, version 16 for Windows (SPSS Inc., Chicago, IL, USA). The difference between groups were tested by one-way analyses of variance (ANOVA) test. Correlations were investigated by means of the Pearson correlation coefficient. Values of p<0.05 were considered statistically significant.

Results

Our study found that both u-desmosine and b-desmosine levels are statistically significantly correlated with age. These correlations were observed in all subjects included in this study (for urine and blood desmosine respectively: COPD patients; r=0.479 and 0.622 Control subjects; r=0.459 and 0.394) (P<0.01 for all groups).

In this study, the patients with stable COPD excreted a higher level of u-desmosine (13.19 ± 2.54) compared with healthy smokers (10 ± 2.91) and non-smokers (8 ± 2.101) (p<0.05). Similar results were found among COPD patients with exacerbation (18.51 ± 2.074) (p<0.01). U-desmosine levels didn’t show a statistically significant difference between healthy smokers and healthy non-smokers (p>0.05). Also, no statistically significant difference was found between non-smokers, current smokers and ex-smokers among the COPD patient groups (p>0.05).

Our work detected that the b-desmosine levels were statistically significantly higher among the patients with stable (0.29 ± 0.045) and exacerbated COPD (0.34 ± 0.034) in comparison with healthy smoker (0.22 ± 0.061) and non-smokers subjects (0.20 ± 0.045) (p<0.01). The b-desmosine levels didn’t show a statistically significant difference between healthy smokers and healthy non-smokers (p>0.05).

We found that the u-desmosine and b-desmosine were statistically significantly higher among exacerbated COPD patients (18.51 ± 2.074 and 0.34 ± 0.034 respectively) in comparison with stable COPD patients (13.19 ± 2.54 and 0.29 ± 0.045 respectively) (p<0.01).
In this work, the levels of u-desmosine and b-desmosine were found to be positively correlated (r=0.679) among all COPD patients (stable COPD patients and exacerbated COPD patients) (p<0.01).

In this work the mean levels of u-desmosine and b-desmosine were statistically significantly higher in patients with severe COPD (17.52 ± 1.65 and 0.31 ± 0.013 respectively) compared with those with mild COPD (12.28 ± 2.67 and 0.27 ± 0.021 respectively) (p<0.05) (Table 3). Also, the mean levels of u-desmosine and b-desmosine were statistically significantly higher in patients with very severe COPD (20.11 ± 1.45 and 0.36 ± 0.038 respectively) in comparison with other severity group patients (p<0.05). Also, u-desmosine and b-desmosine were significantly and inversely correlated with FEV1% (r=-0.828 and -0.795 respectively ) and DLCO% (r=-0.564 and -0.708 respectively ) (p<0.01).

In this study we found that the elevation of b-desmosine levels was found in 69% of all COPD patients (stable COPD and exacerbated COPD) based on a cutoff of 0.30 ng/ml. The area under the curve (AUC) for b-desmosine was 0.731 using the Youden index , the cutoff value for b-desmosine to predict COPD 0.30 ng/ml.This cutoff value had a diagnostic sensitivity of 71% and specificity of 53% (Figures 1-6).

Discussion

Our study found that both u-DES and b-DES levels are statistically significantly correlated with age. These correlations were observed in...
and b-desmosine and some lung function measures (FEV1% and DLCO%). The u-desmosine and b-desmosine were significantly and inversely correlated with FEV1% and DLCO % after adjustment for age, BMI, sex and smoking status. Gottlieb et al. [24] and Lindberg et al. [16] found significantly higher u-desmosine excretion in lower FEV1, and a significant correlation between desmosine excretion and lower FEV1. Another study by Viglio et al. [25] showed a correlation between u-desmosine and FEV1 % in a group of patients with destructive lung disease (cystic fibrosis, bronchiectasis, COPD and a1-antitrypsin deficiency). In contrast, Boutin et al. [26] found significantly lower levels of u-desmosine in COPD patients with lower FEV1. Another study by Ma et al. [9] could not demonstrate any correlation between u-desmosine and various lung function parameters.

In this study we found that the elevation of b-desmosine levels were found in 69 % of all COPD patients based on a cutoff of 0.30 ng/ml. This cutoff value had a diagnostic sensitivity of 71% and specificity of 53%. These findings suggest the elevations of desmosine are not specifically for COPD patients Our results are consistent with that of other researchers. Huang et al. [19] demonstrated that the elevations of b-desmosine levels are specific to approximately 40% of COPD patients. Viglio et al. [25], and [18] they demonstrated that u-desmosine and b-desmosine were much more pronounced in COPD subjects than in those without COPD (Table 1). However, Boutin et al. [26] found significantly lower levels of u-desmosine in COPD patients. Explanations for the different results may be due to the different methods used, sample sizes variations and varying correction for other, potentially confounding factors. Another explanation for inconsistent results between studies could be that the relationship between desmosine and lung function may be different in different populations depending on disease status and severity. However our results are in accord with the pathophysiology of COPD that involves neutrophil-driven inflammation, lung matrix degradation and increased desmosine release [27]. Although elastin is not specific component of the lungs but also serves an important function in the arteries, as a medium for pressure wave propagation to help blood flow, and is particularly abundant in large elastic blood vessels, such as the aorta. Elastin is also important in other tissues, such as elastic ligaments, the skin and the bladder. Therefore, it is possible that degradation from tissues other than the lung may have contributed to the associations seen in this study. However, since many of these tissues are affected in COPD due the systemic inflammation, this may also be relevant to the pathophysiology of the disease. It has also been estimated that the normal rate of lung elastin turnover accounts for only 19% of the desmosine excreted in urine [28].

Conclusions

This study has demonstrated that both u-desmosine or b-desmosine levels were significantly elevated among COPD patients. Also, u-desmosine and b-desmosine levels are correlated with COPD severity and some lung function parameters. This study suggests both u-desmosine or b-desmosine could be a useful biomarker in the diagnosis of COPD patients and to determine COPD severity.

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