Expression and Clinical Significance of Serum Dipeptidyl Peptidase IV Chronic Obstructive Pulmonary Disease

Xiao-Yue Chang, MD, Yong Yang, MD, Xiao-Qing Jia, MD, Yuan Wang, MD, Li-Na Peng, MD, Xiao-Hong Ai, MD, Cui-Ying Jiang, MD, Jian-Hua Guo, MD and Ting-Ting Wu, MD

ABSTRACT

Objective: The purpose of this study is to explore the correlation between serum dipeptidyl peptidase IV (DPPIV) and chronic obstructive pulmonary disease (COPD) at its various disease states, analyze its applications in the prediction and diagnosis of COPD and test the possibility of DPPIV as the serologic marker for COPD screening.

Materials and Methods: Samples from 74 patients (42 cases with acute exacerbation of COPD or acute exacerbation COPD (AECOPD) and 32 cases with stable COPD) and 29 control subjects were collected in this study. Those patients with AECOPD were classified as COPD remission group if their clinical symptoms relieved after nonintravenous or oral hormone therapy for 7 ± 3 days. DPPIV concentration was measured by enzyme-linked immunosorbent assay, and the difference in serum concentration of DPPIV was compared among different groups. The correlation between DPPIV concentration and age, sex or smoking history was analyzed, and the diagnostic value of DPPIV was evaluated by receiver-operating characteristic (ROC) curve analysis.

Results: Serum DPPIV concentration was significantly lower in all COPD groups as compared with that in healthy control group ($P < 0.001$). Serum DPPIV concentration in AECOPD group was increased after treatment ($P < 0.001$). There was no significant correlation between DPPIV concentration and age, sex or smoking history ($P > 0.05$). ROC analysis indicated that serum DPPIV concentration in all groups showed a good diagnostic accuracy, especially in stable COPD and AECOPD groups. The area under the ROC curve values were 0.901 and 0.906, respectively, with a high specificity of 0.931 for both groups and a high sensitivity of 0.75 for stable COPD and 0.875 for AECOPD.

Conclusions: Serum DPPIV concentration in patients with COPD is decreased significantly, and there is no correlation between serum DPPIV concentration and sex or age. Serum DPPIV not only is an independent predictive factor, but also of high value as a good serologic marker for the diagnosis of COPD.

Key Indexing Terms: Dipeptidyl peptidase IV; Chronic obstructive pulmonary disease; Inflammation; Lymphocytes. **[Am J Med Sci 2016;351(3):244–252.]**

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) refers to a group of respiratory diseases characterized by persistent airflow limitation that is progressive and not fully reversible.[1] The pathogenesis of COPD is the increased chronic inflammation mainly caused by several risk factors, including smoke, dust and other harmful substances. The most significant risk factor for COPD is long-term cigarette smoking.[2,3] Currently, the diagnosis of COPD mainly depends upon pulmonary function tests,[1] and there are no reliable serologic markers that might be helpful in diagnosis and prediction of the disease progression.

Dipeptidyl peptidase IV (DPPIV), also known as CD26, is a homodimer on the cell surface and is a catalytically active protease. It is a multifunctional cell surface protein that is widely expressed in most cell types including T lymphocytes, on which it is a marker of activation.[4] Serum DPPIV is a naturally occurring soluble truncated form of DPPIV without transmembrane and intracellular domains. The soluble form of the protein is present in the serum and other extracellular body fluids, including saliva, semen and bile, presumably as a result of shedding or secretion from different cell types.[5] DPPIV/CD26 is able to inactivate a variety of factors, including neuropeptides, peptide hormones and chemokines.[6] In addition, DPPIV/CD26 decreases the levels of Th2 cytokines interleukin (IL)-4, IL-5, as well as isotypes IgG1, whereas increases the levels of Th1 cytokines IL-2, tumor necrosis factor-α, interferon-γ, and isotypes IgG2a.[7] Therefore, the Th1/Th2 balance is modulated and shifted toward the Th1 phenotype. DPPIV/CD26 reduces the damage to the body by inactivation of inflammatory chemokines and avoiding excessive inflammatory response. Even though chemokines play a protective role in the inflammation, excessive accumulation of chemokines-induced inflammatory cells at sites of inflammation tends to cause local damage.

Furthermore, DPPIV/CD26 plays an important role in tumor biology as a suppressor in the development of

cancer and is a useful biomarker for different cancers, with an elevated or reduced levels on the cell surface or in the serum dependent upon the involved cancers.[8-10] In addition, DPPIV also plays an important role in metabolism, especially glucose metabolism. For example, DPPIV is responsible for the degradation of glucagon-like peptide-1 (GLP-1).[11]

It is reasonable to suppose that DPPIV, being able to inactivate inflammatory chemokines and avoid excessive inflammatory response, plays a role in COPD and other inflammatory diseases. Indeed, Schade et al[12] found that DPPIV plays an important role in the inflammatory response in the lungs. Recently, it has been shown that the serum DPPIV activity in patients with stable COPD is significantly lower than that in healthy people, and it is not affected by smoking, age and other factors, suggesting that serum DPPIV activity might be a valuable serologic marker for COPD.[13]

In the present study, we hypothesized that serum DPPIV concentration may be an important marker for COPD, in particular, for the differential diagnosis and prognosis of different COPD. To address this problem, serum DPPIV concentration was determined with enzyme-linked immunosorbent assay (ELISA) method in 4 groups, that is, the stable COPD group, acute exacerbation COPD (AECOPD) group, remission groups (patients with AECOPD alleviated after appropriate treatment) and healthy control group. The difference in serum DPPIV levels among different groups was compared and correlation between serum DPPIV levels and the diagnosis and progression of COPD was analyzed.

MATERIALS AND METHODS

Materials

A total of 42 patients, 33 men and 9 women, aged 68 years (ranged: 49-81 years), 28 smokers and 14 nonsmokers, diagnosed with AECOPD, were enrolled in this study. All patients, either outpatients or inpatients, were referred to the Department of Respiratory Medicine, Baotou Central Hospital from January to December 2013. Those patients with clinical remission after treatment with intravenous or oral hormone therapy for 7 ± 3 days were classified as COPD remission group (42 patients). Patients would be withdrawn from the study automatically if higher dosage of hormone therapy was required. In total, 32 patients were diagnosed with COPD, 25 men and 7 women, aged 64 years (ranged: 46-79 years), 26 smokers and 6 nonsmokers, have visited Department of Respiratory Medicine for treatment and been followed up and stable for more than 3 months without acute exacerbation. These patients were classified as stable COPD group. A total of 29 healthy volunteers, 15 men and 14 women, aged 65 years (ranged: 45-80 years), 16 smokers and 13 nonsmokers, were recruited as control subjects from Baotou Central Hospital during the same period of time. Pulmonary functions were tested for the control subjects to exclude those with respiratory abnormalities. Smokers and nonsmokers were defined as having a smoking index (cigarettes smoked per day $\times$ years smoked) of >0.5 and ≤ 0.5, respectively.[14]

The diagnosis of COPD was based on Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Revised 2011).[15] The criteria for stable COPD in this study were that there have been no acute exacerbation, no medium to severe respiratory disease-related symptoms, such as cough, sputum, shortness of breath, or wheezing for more than 3 months. Metabolic diseases, rheumatoid diseases, blood diseases and history of cancers were excluded for all subjects. In addition, all subjects were not treated with steroid hormone therapy orally or intravenously in the recent 30 days (inhaled steroids allowed). This study was approved by the Ethics Committee of Baotou Central Hospital and all subjects signed informed consent.

TABLE 1. Basic information of the participants.

Variable	Healthy control $n = 29$	Stable COPD $n = 32$	AECOPD $n = 42$	COPD remission $n = 42$	*P* Value
Age (year)	65 (45-80)	64 (46-78)	69 (49-80)	—	0.051
Sex	M = 15, F = 14	M = 25, F = 7	M = 33, F = 9	—	0.028
WBC count ($\times 10^9$/L)	6.59 (5.27–7.36)	6.15 (5.83–7.40)	8.01 (6.27–9.16)	6.86 (5.18–8.50)	0.000
Neutrophils/WBC (%)	56.4 (52.1–60.4)	66.7 (62.0–73.7)	69.5 (62.9–75.7)	65.5 (57.0–69.5)	0.000
Neutrophils ($\times 10^9$/L)	3.60 (3.05–4.31)	4.10 (3.70–4.99)	5.42 (4.28–6.77)	4.56 (3.68–5.58)	0.000
Lymphocytes/WBC (%)	32.8 (30.2–36.6)	24.8 (19.8–28.2)	18.5 (14.1–26.5)	24.1 (19.0–29.0)	0.000
Lymphocytes ($\times 10^9$/L)	2.18 (1.70–2.49)	1.54 (1.23–1.98)	1.59 (1.10–1.95)	1.75 (1.26–2.05)	0.000
FEV1/FVC (%)	79 (77–86)	46 (39–56)	58 (50–65)	–	0.000
FEV1/predicted value (%)	97.0 (91.5–105.0)	48.0 (34.5–59.5)	51.9 (37.8–69.1)	–	0.000

Note: the median and interquartile are expressed as M (Q1-Q3); $\alpha = 0.05$ and *P* values represent comparisons of multiple independent samples (healthy control, stable COPD, AECOPD and COPD remission). FEV1/FVC, forced expiratory volume in 1 second/forced vital capacity.

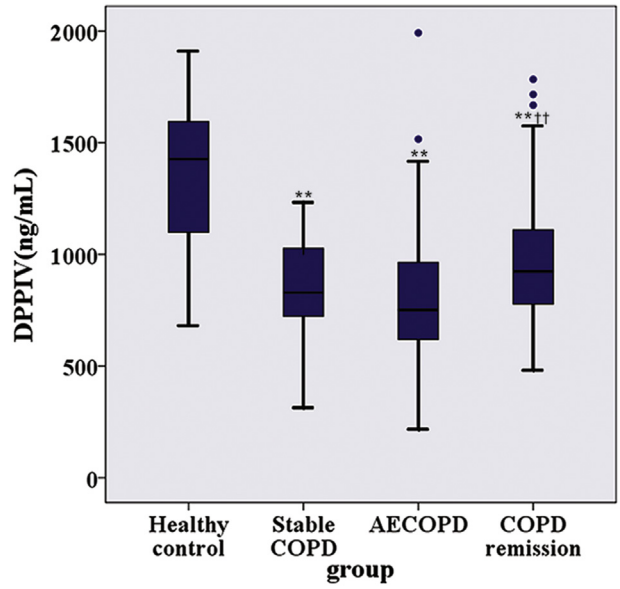

FIGURE 1. Serum concentrations of DPPIV. The top of the box represents the 75th percentile and the bottom represents the 25th percentile. The line in the middle represents the median. The whiskers represent the 10th and 90th percentiles. Outliers are represented by circles beyond the whiskers. Kruskal-Wallis *H* test is used to compare the differences in serum DPPIV between healthy control group and COPD groups, including stable COPD, AECOPD and COPD remission groups. $^{**}P < 0.001$ for stable COPD, AECOPD and COPD remission versus Healthy control; $^{\dagger\dagger}P < 0.001$ for COPD remission versus AECOPD.

Methods

Pulmonary Function Tests

All the subjects were subjected to the tests performed by the same senior technician with Quark PFT 4 (Cosmed, Milan, Italy).

Serum Specimen Collection and Handling

Fasting blood samples were collected in the early morning. Blood samples were kept for 1 hour at room temperature (22-24°C) and centrifuged at 3000 rpm/minute for 10 minutes. The resulting supernatant was designated serum and aliquoted and stored at −20°C until the measurements of DPPIV.

Routine Blood Tests

All the blood samples were tested within 2 hours in Baotou Central Hospital Testing Center with the XE-5000 automated hematology analyzer.

Determination of Serum DPPIV

Serum level of DPPIV was measured using ELISA reagents from Cloud-Clone Corp (Wuhan branch). Sera were diluted 2000-fold and assays were performed according to the manufacturer's instructions. The optical density value was determined at 450 nm using a Multiskan MK3 microplate reader (Thermo Electron, Waltham, USA).

Statistical Analysis

All statistical analyses were performed with the SPSS Statistics 17.0. Normally distributed data were

TABLE 2. Comparison of serum level of DPPIV in different groups.

Pairwise comparison	$\lvert\bar{R}i-\bar{R}j\rvert$	Z_{ij} value	*Z* value	*H* value	*P* Value
Healthy control vs. stable COPD	24.45	−5.372	–	–	0.000
Healthy control vs. AECOPD	28.82	−5.785	–	–	0.000
COPD vs. AECOPD	5.92	−1.173	–	–	0.241
Healthy control vs. COPD remission	22.33	−4.480	—	–	0.000
Stable COPD vs. COPD remission	7.84	−1.555	–	–	0.120
AECOPD vs. COPD remission	–	–	−3.507	–	0.000
Healthy control, stable COPD, AECOPD	–	–	–	41.119	0.000

Note: Kruskal-Wallis *H* test is used to compare healthy control, stable COPD and AECOPD groups; rank sum test is used to perform pairwise comparison among groups; Wilcoxon signed-rank test is used to compare the serum level of DPPIV before and after treatment in AECOPD group.

TABLE 3. Comparison of serum level of DPPIV in smokers and nonsmokers.

Smokers/nonsmokers	DPPIV (ng/mL)	*F* value	*t* value	*P* Value
Healthy control	1427 (1080–1620)	2.112	0.312	0.757
Stable COPD	828 (722–1037)	0.030	−1.649	0.110
AECOPD	751 (610–966)	0.610	0.281	0.780

expressed as mean ± standard deviation and non-normally distributed data were expressed as median with interquartile range.

A single-factor analysis of variance was used when multiple sets of measurement data followed a normal distribution and homogeneity of variance under the same conditions. SNK-q (Student-Newman-Keuls) test was employed to compare the difference among groups. Alternatively, Kruskal-Wallis *H* test was used under heterogeneity of variance. In this case, pairwise comparisons were performed with Wilcoxon rank test. Chi-square (χ^2) test for comparisons of multiple samples was carried out in a row × column contingency table. The Wilcoxon signed-rank tests were used to analyze the data from groups of patients before and after treatments. Pearson correlation analysis was used for bivariate normal distributions, receiver-operating characteristic (ROC) curve analysis was used to evaluate the diagnostic value and Logistic regression analysis was used to study the relationship between various parameters and COPD.

RESULTS

Basic Information of the Participants

The demographic data of all subjects are listed in Table 1. It was shown that there were significant differences in white blood cells (WBC) count, neutrophil count, lymphocyte count, lymphocyte ratio, neutrophil ratio and pulmonary function indicators among the 4 different groups (healthy control group and 3 different groups of COPD). These differences might be the results of the differences in each group. Analysis of variance showed that there was no statistically significant difference in age among healthy control group, stable COPD group and AECOPD group ($P > 0.05$). However, there was a significant difference in sex composition among groups ($P < 0.05$).

Serum DPPIV in Patients With COPD

Serum concentrations of DPPIV in different groups were summarized in Figure 1 and Table 2. Pairwise comparison showed that there was significant difference in serum levels of DPPIV between healthy control group and stable COPD group, and between healthy control group and AECOPD groups ($P < 0.001$), and that the decreased serum DPPIV had little to do with the state of the disease. However, there was no difference in serum levels of DPPIV between stable COPD and AECOPD ($P > \alpha'$).

The difference in serum level of DPPIV in patients with AECOPD before and after treatment was further compared with Wilcoxon signed-rank test and the results showed that the *Z* value was −3.507 with a 2-tailed probability of $P < 0.001$, suggesting that serum level of DPPIV in patients with AECOPD after treatment was higher than before treatment (with $\alpha = 0.05$) (Table 2). There was a significant decrease in serum level of DPPIV in COPD remission group as compared with that in healthy control group ($P < 0.001$). Even though the serum level of DPPIV in COPD remission group was slightly increased as compared with that in stable COPD group, the difference was of no statistical significance (Table 2).

Tobacco smoking, the major risk factor of COPD, had no effect on serum level of DPPIV in all tested groups (Table 3) ($P > 0.05$). As shown in Tables 4 and 5 there was no relationship between serum level of DPPIV and age and sex ($P > 0.05$).

Serum DPPIV as a Potential Marker for COPD

Since serum levels of DPPIV were reduced significantly in all COPD groups, it is of considerable interest to ask whether serum DPPIV could be used clinically as a marker for the diagnosis of COPD. To this end, ROC analysis, a useful tool for evaluating the performance of

TABLE 4. Correlation analysis between serum level of DPPIV and age.

Groups	Serum DPPIV (ng/mL)	Age (years)	*r* value	*P* Value
(1) Healthy control[a]	1427 (1080–1620)	65 (45–80)	0.073	0.706
(2) Stable COPD[a]	828 (722–1037)	64 (46–78)	0.062	0.734
(3) AECOPD	751 (610–966)	69 (49–80)	0.070	0.658
(4) COPD remission	924 (776–1112)	69 (49–80)	0.023	0.885
(1) + (2) + (3)	937 (696–1189)	67 (45–80)	−0.112	0.259
(1) + (2) + (4)	1010 (785–1241)	67 (45–80)	−0.130	0.900

[a] The results of Pearson correlation analysis as data in these groups follow the bivariate normal distribution. The rest of the data represent the results of Spearman rank correlation analysis.

TABLE 5. Comparison of serum level of DPPIV in men and women.

Men/women	DPPIV (ng/mL)	*F* value	*t* value	*P* Value
Healthy control	1427 (1080–1620)	1.765	0.980	0.336
Stable COPD	828 (722–1037)	1.112	0.238	0.813
AECOPD	751 (610–966)	2.536	0.245	0.808

diagnostic tests, was employed for further analysis. As shown in Table 6 and Figures 2-5, serum levels of DPPIV in all COPD groups showed a very good diagnostic accuracy, reflected by high area under the ROC curve (AUC) values of greater than 0.8 in all COPD groups. In particular, the AUC values were 0.901 and 0.906 in stable COPD and AECOPD groups, respectively, indicating a high diagnostic accuracy.

Serum Level of DPPIV and Lymphocytes

In this section, the COPD remission group and stable COPD group were merged into 1 group for further analysis considering the relative small sample size in each group, and there was no statistically significant difference in serum concentration of DPPIV. Multiple logistic regression analysis was performed to analyze the potential relationship between serum level of DPPIV and each of the following 6 factors: WBC count, lymphocyte count, the lymphocyte/WBC ratio, neutrophil count and neutrophil/WBC ratio (Table 7). Regression equation obtained was $\text{logit}P = 7.282 + 1.382X_1 - 2.452X_2 - 0.006X_3$. Where X_1 and X_2 were neutrophil count and lymphocyte/WBC ratio, respectively, and X_3 was serum level of DPPIV. $\chi^2 = 60.695$ with $P = 0.000$ was obtained, indicating that the regression equation was statistically significant. However, it should be noted that there were no significant relationships between WBC, lymphocytes, neutrophil/WBC ratio and COPD (Table 7).

Based on logistic regression analysis, serum level of DPPIV, lymphocyte/WBC ratio and neutrophil count could be considered as the independent predictors in COPD. However, scatter plot did not show a clear linear relationship between serum level of DPPIV and lymphocytes in any given groups. The same conclusion was obtained with a quadratic curve fitting ($r < 0.2$).

DISCUSSION

Even though it has been reported that DPPIV plays an important role in experimental asthma[16] and that serum DPPIV activity is decreased in patients with stable COPD,[13] the exact relationship between serum DPPIV and COPD is unknown. In this article, the principal novelties were that we systematically investigated for the first time the correlation between serum level of DPPIV and various types of COPD, including stable COPD, AECOPD and COPD remission group, by directly measuring serum concentrations of DPPIV with ELISA, followed by a comprehensive analysis of the relationships between a set of parameters of COPD and different forms of COPD using different statistical analysis methods. Overall, by directly measuring the serum level of DPPIV, a better ROC results were obtained, and our results not only extended and complemented the existing knowledge regarding the relationship between DPPIV and COPD, but also expanded the idea of screening novel COPD biomarkers.

The results of the present study showed that serum levels of DPPIV were significantly decreased in both stable COPD and AECOPD. Similar results have been reported in recent years, for example, Somborac-Bačura et al[13] found a significant reduction in serum DDPIV activity in patients with stable COPD. With immunohistochemistry staining and direct measurement of serum level of DPPIV, Landis et al[17] reported that DPPIV/CD26 is decreased and is inversely correlated with the degree of airway inflammation in patients with chronic bronchitis. In addition, our study also found that serum level of DPPIV in patients with AECOPD whose condition have been improved after appropriate treatment increased slightly, suggesting that with the reduction in airway inflammation and the improvement of the general condition of the patients, DPPIV level tended to increase, and that serum level of DPPIV might be used for the

TABLE 6. Results of ROC analyses.

Groups	AUC	95% CI		Critical value for DPPIV (ng/mL)	Sensitivity	Specificity	Standard error	*P* Value
		Lower limit	Upper limit					
(1) COPD stable	0.901	0.822	0.979	1008.602	0.750	0.931	0.040	0.000
(2) AECOPD	0.906	0.832	0.980	1006.738	0.875	0.931	0.038	0.000
(3) COPD remission	0.814	0.713	0.916	1149.745	0.833	0.724	0.052	0.000
(1) + (2) + (3)	0.871	0.801	0.942	1008.602	0.733	0.931	0.036	0.000

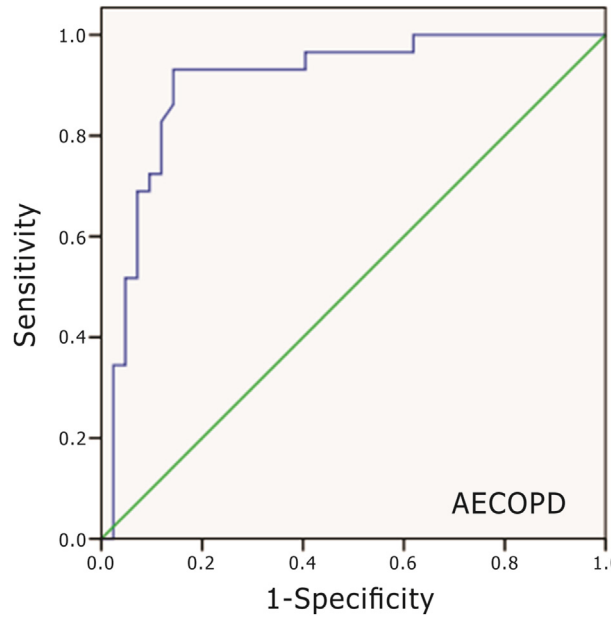

FIGURE 2. ROC curves for AECOPD group.

determination of the effectiveness of COPD treatment. Lun et al[16] reported that serum level in DPPIV is increased significantly in adult patients with allergic asthma, a different inflammatory respiratory disease. Therefore, serum level of DPPIV could also be used potentially to help the differential diagnosis of different respiratory inflammatory diseases.

It has been well known that exposure to tobacco smoke and age are 2 of the major risking factors for COPD. Somborac-Bačura et al[13] reported that DPPIV activity is independent of smoking history and age of patients. Similarly, Chiara et al[18] also reported by a large sample study that there is no correlation between serum levels of DPPIV and patients' age. Our results not only confirmed the aforementioned conclusion that serum levels of DPPIV in patients with COPD or healthy controls have no relevance to smoking history, age and sex, but also extended the conclusion by demonstrating

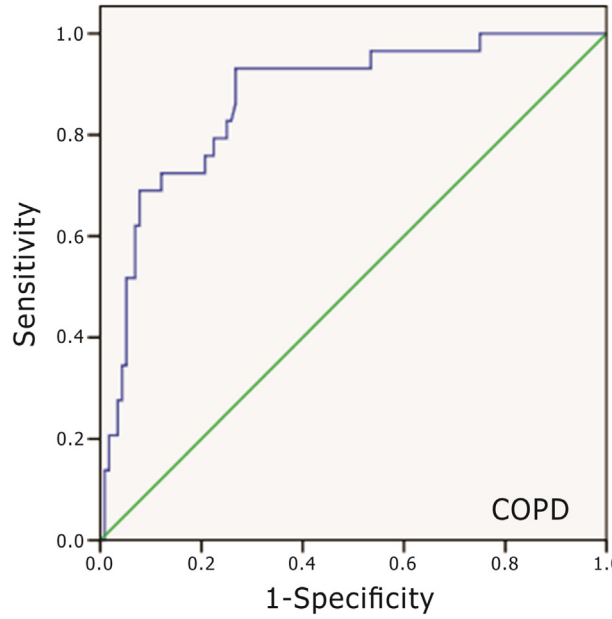

FIGURE 3. ROC curves for COPD group.

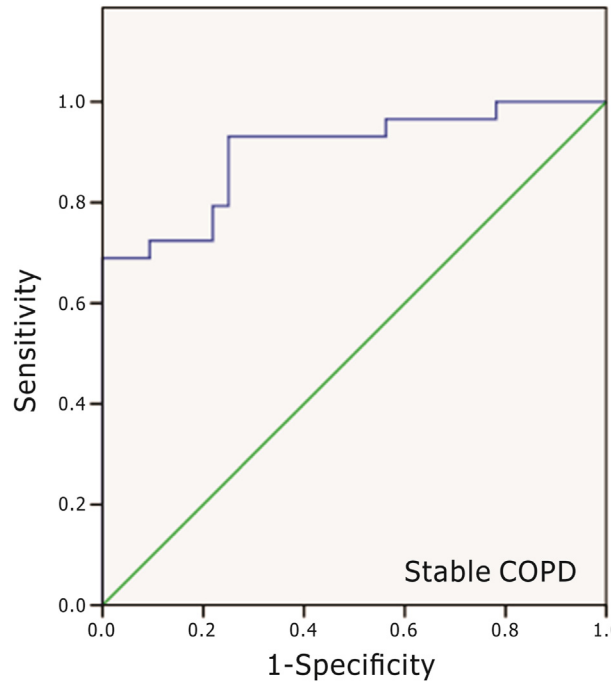

FIGURE 4. ROC curves for stable COPD group.

that there was no correlation between serum levels of DPPIV and patients' smoking history, age and sex in all subgroups of patients with COPD, that is, AECOPD group, COPD remission group, stable COPD group and healthy control group. In addition, the diagnostic value of serum levels of DPPIV in patients with COPD was further analyzed with the ROC curve analysis, and it was found that serum levels of DPPIV were of a high diagnostic accuracy and that serum DPPIV might be a valuable serologic biomarker for the diagnosis of patients with

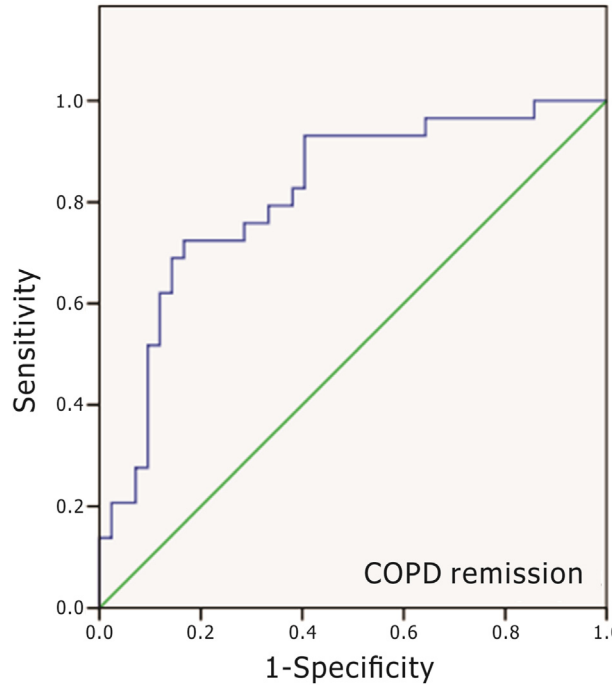

FIGURE 5. ROC curves for COPD remission group.

TABLE 7. Summary of logistic regression.

Variables	*B*	S.E.	Wald	*P* Value	OR	OR 95% CI	
						Lower limit	Upper limit
X_1—neutrophil count	1.382	4.330	10.180	0.001	3.985	1.704	9.316
X_2—lymphocyte/WBC ratio	−2.452	0.700	12.288	0.000	0.086	0.022	0.339
X_3—DPPIV concentration	−0.006	0.002	15.876	0.000	0.996	0.991	0.997

OR, odds ratio; *B*, the regression coefficient of maximum likelihood estimate; S.E., standard error of the estimate.

COPD, especially those with acute exacerbation of COPD and stable COPD, reflected by the high AUC up to 0.906 and 0.901 for AECOPD group and stable COPD group, respectively.

As an independent predictor for patients with COPD, the effect of serum DPPIV might be associated with the T lymphocyte-related immune response. Using CD26 knockout mice, Yan et al[19] demonstrated that DPPIV/CD26 has a protective role in restricting ovalbumin-induced airway inflammation, reflected by the significantly reduced serum IgG, including IgG1 and IgG2a subclasses, and the increased expression of Th2 cytokines IL-4, IL-5, and IL-13 at both mRNA and protein levels, as well as the expression of chemokines eotaxin, RANTES and their receptor CC chemokine receptor 3 (CCR3) and CCR5 in $CD26^{-/-}$ mice. With the logistic regression analysis, we also believed that serum level of DPPIV and the lymphocyte/WBC ratio are independent predictors in COPD.

In patients with COPD, the inactivation of inflammatory chemokines decreases because of the decrease in serum levels of DPPIV/CD26, resulting in accumulation of a large number of inflammatory cells and inflammatory factors in the airway tract, leading to airway wall thickening, remodeling, and small airways obstruction and incomplete reversible changes in structure and function of the airways, accompanied by a variety of extrapulmonary effects, such as skeletal muscle atrophy, osteoporosis, malnutrition, repeated worsening of clinical symptoms, decreased exercise tolerance and reduced quality of life.

Recently, various types of DPPIV inhibitors have been developed as potential new drugs for the treatment of diseases such as diabetes,[20] with some of them available in markets. It should be noted, however, that DPPIV inhibitors can induce arthritis[21,22] because of their immunosuppressive effects.[23] In addition, it has been reported that DPPIV inhibitors cause coughing, shortness of breath and difficulty breathing in patients with type 2 diabetes mellitus.[24] Based on our studies, careful attention should be paid to the treatment of those patients with diabetes mellitus accompanied with COPD with DPPIV inhibitors as serum levels of DPPIV are already lowered in these patients and DPPIV inhibitors may potentially aggravate COPD.

CONCLUSIONS

The main conclusions are that serum level of DPPIV is not associated with smoking history, sex and age. DPPIV is an independent predictor in patients with COPD and maybe a valuable serologic biomarker for the diagnosis and differential diagnosis of COPD. Further investigations are needed to (1) expand the sample size by clinical studies as only 1 published article is available regarding the relationship between serum DPPIV and COPD; (2) perform experimental studies to explore the underlying mechanisms and perform experimental therapeutic studies.

REFERENCES

1. ***Global Strategy for the Diagnosis, Management and prevention of Chronic Obstructive Pulmonary Disease.*** Global Initiative for Chronic obstructive Lung Disease (GOLD). Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf; 2013.
2. **Burney P, Jithoo A, Kato BE, et al.** Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty—a BOLD analysis. Thorax 2014;69:465–73.
3. **Eisner MD, Anthonisen N, Coultas D, et al.** An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693–718.
4. **De Meester I, Korom S, Van Damme J, et al.** CD26, let it cut or cut it down. Immunol Today 1999;20:367–75.
5. **Durinx C, Lambeir AM, Bosmans E, et al.** Molecular characterization of dipeptidyl peptidase activity in serum: soluble CD26/dipeptidyl peptidase IV is responsible for the release of X-Pro dipeptides. Eur J Biochem 2000;267(17):5608–13.
6. **Ohnuma K, Dang NH, Morimoto C.** Revisiting an old acquaintance: CD26 and its molecular mechanisms in T cell function. Trends Immunol 2008;29:295–301.
7. **Delgado M, Leceta J, Gomariz RP, et al.** Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide stimulate the induction of Th2 responses by up-regulating B7.2 expression. Immunol 1999;163:3629–35.
8. **Larrinaga G, Blanco L, Sanz B, et al.** The impact of peptidase activity on clear cell renal cell carcinoma survival. Am J Physiol Renal Physiol 2012;303:F1584–91.
9. **Cordero OJ, Salgado FJ, Nogueira M.** On the origin of serum CD26 and its altered concentration in cancer patients. Cancer Immunol Immunother 2009;58:1723–47.
10. **Javidroozi M, Zucker S, Chen WT.** Plasma seprase and DPP4 levels as markers of disease and prognosis in cancer. Dis Markers 2012;32:309–20.
11. **Holst JJ, Deacon CF.** Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. Diabetologia 2005;48:612–5.
12. **Schade J, Stephan M, Schmiedl A, et al.** Regulation of expression and function of dipeptidyl peptidase 4 (DP4), DP8/9, and DP10 in allergic responses of the lung in rats. J Histochem Cytochem 2008;56:147–55.
13. **Somborac-Bačura A, Buljević S, Rumora L, et al.** Decreased soluble dipeptidyl peptidase IV activity as a potential serum biomarker for COPD. Clin Biochem 2012;45:1245–50.
14. **World Health Organisation.** Guidelines for Controlling and Monitoring the Tobacco Epidemic. Geneva: Tobacco or Health Programme, WHO; 1997.

15. **GOLD Executive Commitee**. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Revised 2011)*. www.goldcopd.com.
16. **Lun SW, Wong CK, Ko FW, et al.** Increased expression of plasma and CD4+ T lymphocyte costimulatory molecule CD26 in adult patients with allergic asthma. J Clin Immunol 2007;27:430–7.
17. **Landis BN, Grouzmann E, Monod E, et al.** Implication of dipeptidyl-peptidase IV activity in human bronchial inflammation and in bronchoconstriction evaluated in anesthetized rabbits. Respiration 2008;75:89–97.
18. **De Chiara L, Rodríguez-Piñeiro AM, Cordero OJ, et al.** Soluble CD26 levels and its association to epidemiologic parameters in a sample population. Dis Markers 2009;27:311–6.
19. **Yan S, Genner R, Dietel C, et al.** Enhanced ovalbumin-induced airway inflammation in CD26$^{-/-}$ mice. Eur J Immunol 2012;42:533–40.
20. **Ji X, Su M, Wang J, et al.** Design, synthesis and biological evaluation of hetero-aromatic moieties substituted pyrrole-2-carbonitrile derivatives as dipeptidyl peptidase IV inhibitors. Eur J Med Chem 2014;75C:111–22.
21. **Crickx E, Marroun I, Veyrie C, et al.** DPP4 inhibitor-induced polyarthritis: a report of three cases. Rheumatol Int 2014;34:291–2.
22. **Jojima T, Aso Y.** Attention to the use of oral anti-diabetic medication in older adults with type 2 diabetes. Nihon Rinsho 2013;71:1987–92.
23. **Saito T, Ohnuma K, Suzuki H, et al.** Polyarthropathy in type 2 diabetes patients treated with DPP4 inhibitors. Diabetes Res Clin Pract 2013;102:e8–12.
24. **Lauster CD, McKaveney TP, Muench SV.** Vildagliptin: a novel oral therapy for type 2 diabetes mellitus. Am J Health Syst Pharm 2007;64:1265–73.

From the Department of Respiratory Medicine (X-YC, YY, X-QJ, YW, L-NP, X-HA, C-YJ, J-HG), Baotou Central Hospital, Donghe District, Baotou, China; Department of Nephrology Medicine (T-TW), Baotou Central Hospital, Donghe District, Baotou, China.

Submitted June 26, 2015; accepted October 26, 2015.

There are no ethical/legal conflicts involved in the article.

Funded by the Social Development Support Project in Baotou, Code: 2014S2003-1-9.

Correspondence: Yong Yang, MD, Baotou Central Hospital, Department of Respiratory Medicine, 61 Ring Road, Donghe District, Baotou, Inner Mongolia China (E-mail: snicl@qq.com).