European Review for Medical and Pharmacological Sciences 2018; 22: 6463-6468

The expressions and significance of APN, D-D, IL-17 and hs-CRP in patients with acute exacerbation of chronic obstructive pulmonary disease

G.-Z. DING, W.-S. LI

Department of Respiratory Medicine, Anqing Municipal Hospital, Anqing, Anhui, China

Abstract. – OBJECTIVE: Inflammatory reactions and imbalance of oxidant/antioxidant and protease/anti-protease are the major causes of chronic obstructive pulmonary disease. Based on the information mentioned, the expressions and significance of adiponectin (APN), D-dimer (DD), Interleukin (IL)-17, and high-sensitivity CRP (hs-CRP) in patients with acute exacerbation of chronic obstructive pulmonary disease were investigated in this study.

PATIENTS AND METHODS: A total of 70 patients with chronic obstructive pulmonary disease were enrolled and divided into stable group (group A, 28 cases) and acute exacerbation group (group B, 42 cases). Thirty-five healthy volunteers were included in the control group (group C, 35 cases). The levels of serum APN, IL- 17, D-D, and hs-CRP were tested and compared

RESULTS: Levels of APN from Group B were significantly lower than that of Group A or Group C, while levels of APN of Group A were also significantly lower than that of Group C, ($p < 0.05$). Levels of IL-17, D-D, and Hs-CRP of group b were significantly increased compared to that of Group A or Group C, and levels of IL-17, D-D, and Hs-CRP of Group A were significantly elevated compared to that of Group C ($p < 0.05$). A negative statistical correlation was found between APN and IL-17, D-D, and Hs-CRP ($p < 0.05$).

CONCLUSIONS: Levels of APN were downregulated in patients with acute exacerbation of chronic obstructive pulmonary disease. The expression levels of APN, IL-17, D-D, and Hs-CRP were closely correlated with clinical stages and can be used as parameters for the evaluation of the severity of chronic obstructive pulmonary disease.

Key Words:
Inflammatory factors, Chronic obstructive pulmonary disease, Expression.

Introduction

Chronic obstructive pulmonary disease (COPD) represents a type of devastating chronic airway inflammatory disease which is currently preventable and treatable. However, the prevalence and mortality of COPD remain high, leading to a greater economic burden[1,2]. Basically, COPD is a progressive, abnormal inflammatory response of the lung to noxious particles or gases. Although COPD is an airway disease, it also affects the patient's physical and mental health and the impact of COPD on another system cannot be ignored[3,4]. Drug treatment can only relieve clinical symptoms of patients with COPD[5,6]. Therefore, the pathogenesis of the disease and its risk factors are of great clinical significance and can provide a theoretical reference for the prevention and treatment of COPD. In this study, 70 patients with COPD and 35 healthy control were included, while the expressions and clinical significance of Adiponectin (APN), D-dimer (DD), Interleukin (IL)-17, and high-sensitivity CRP (hs-CRP) in patients with acute exacerbation of COPD were investigated.

Patients and Methods

Patients

A total of 28 patients with stable COPD from January 2016 to January 2017 were included in group A. Another 42 patients with acute exacerbation of COPD from January 2016 to January 2017 were included in group B. Thirty-five healthy volunteers were included as controls (Group C). Inclusion criteria are as

Corresponding Author: Wusheng Li, MD; e-mail: sxesmzt1vw@sina.com

follows: (1) willing to accept the spirometry and bronchial challenge test; (2) sign written informed consent; (3) approved by the Medical Ethics Committee. Exclusion criteria: (1) suffering from inflammatory diseases; (2) having diseases of heart, liver, or other organs important; (3) taking immunosuppressive drugs; (4) patients who are pregnant, breastfeeding or too old; (5) having mental diseases; (6) presence of communication disorders. No significant difference was found in gender and age among 3 groups ($p > 0.05$). All the participants were adequately informed about the details of this study and signed the informed consent forms prior to the tests. This study strictly adhered to the requirements of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Anqing Municipal Hospital (Anqing, Anhui, China).

Observation Parameters Levels of APN, IL-17, D-D, and hs-CRP for Each Group Were Measured and Recorded

Six milliliters of fast blood was drawn from the cubital vein for each patient, centrifuged at 3000 g for 30 min, and kept at -80°C for further use. Levels of APN and IL-17 were measured using commercial ELISA kits (Shanghai Rui Cong Laboratory Equipments, Shanghai Huole Biological Technology Co., Shanghai, China). The level of D-D was measured using colloidal gold kit (Shanghai Aopu Biological Pharmaceutical, Shanghai, China). The level of hs-CRP was measured using scattering turbidimetry (Toshiba TBA-40 Automatic Biochemical Analyzer, Minato, Japan).

Statistical Analysis

SPSS19.0 statistical software (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for data analysis. Continuous data are presented as means ± standard deviation (SD) and were analyzed by using one-way ANOVA, with the Tukey's post hoc test. Receiver operating characteristic (ROC) curve analysis was performed in the comparison between patients with stable COPD and with acute exacerbation of COPD. $p < 0.05$ was considered statistically significant.

Results

General Information

The general information of 3 groups was shown in Table I. In group A, there were 15 males and 13 females with an average age of 50.65 ± 8.19 years and a mean disease duration of 12.68 ± 4.49 years. In group B, there were 23 males and 19 females with an average age of 50.47 ± 8.54 years and a mean disease duration of 13.57 ± 4.72 years. In group C, there were 21 males and 14 females with an average age of 50.53 ± 8.25. No significant difference was found in age, gender, or disease duration ($p > 0.05$).

Expression levels of APN, IL-17, D-D, and hs-CRP

Comparative analysis of the levels of APN, IL-17, D-D, and hs-CRP was shown in Table II and Figure 1. Of note, the expression of APN of group B (6.34 ± 0.53 ng/L) was significantly lower than that of group A (8.16 ± 0.54 ng/L), which was also significantly lower than that of group C (8.99 ± 0.51 ng/L). In contrast, the expression levels of IL-17, D-D, and hs-CRP of group B were significantly higher than that of group C, which were significantly higher than that of group A ($p < 0.05$). ROC curve analysis further indicated that APN, IL-17, D-D, and hs-CRP presented the potential diagnostic ability to evaluate acute exacerbation of COPD, the area under the curve (AUC) of which were ranging from 0.758 to 0.885 (Table III).

Table I. General information of all patients ($\bar{x} \pm s$).

Group	Case	Male/female	Age (years)	Duration (years)
A	28	15/13	50.65 ± 8.19	12.68 ± 4.49
B	42	23/19	50.47 ± 8.54	13.57 ± 4.72
C	35	21/14	50.53 ± 8.25	—
F/t/χ^2		0.319	0.039	0.835
p		0.852	0.976	0.738

Table II. Expression levels of APN, IL-17, D-D, and hs-CRP ($\bar{x} \pm s$).

Group	Case	APN (ng/L)	IL-17 (ng/L)	D-D (μg /L)	hs-CRP (mg/L)
A	28	8.16 ± 0.54	39.83 ± 15.14	475.64 ± 114.76	15.45 ± 3.59
B	42	6.34 ± 0.53★	64.95 ± 14.35★	675.84 ± 122.93★	24.37 ± 3.86★
C	35	8.99 ± 0.51★▲	30.81 ± 11.66★▲	261.26 ± 96.45★▲	2.58 ± 1.25★▲
F		19.359	25.802	36.956	33.974
p		0.000	0.0000	0.000	0.000

★$p < 0.05$, compared with Group A; ▲$p < 0.05$, compared with Group B.

Correlation Between APN and IL -17, D-D, and hs-CRP

Statistical analysis results showed that the expression of APN was negatively correlated with the levels of IL -17, D-D, and hs-CRP ($p < 0.05$) (Table IV).

Discussion

The clinical symptoms of patients with acute exacerbation of COPD were much more severe than that of patients with stable COPD, which even lead to the loss of work ability of patients[5,6]. At present, the pathogenesis of COPD has not been fully elucidated. Inflammation and imbalance of protease/anti-protease or oxidant/antioxidant are thought to be the main causes[7,8]. In recent years, it has been found that APN has protective effects against metabolic syndrome, type 2 diabetes, and coronary atherosclerotic heart disease[9,10]. Therefore, we investigated the role of APN in COPD. Results showed that the expression of APN patients with acute exacerbation of COPD was significantly reduced compared to that of patients with stable COPD, which was also significantly lower than that of normal control. Similarly, using 60 patients with acute exacerbation of COPD from January 2010 to July 2010 and 60 healthy controls, Singh et al[7] found that APN level was decreased in patients with acute exacerbation of COPD and the level of APN was positively correlated with arterial oxygen pressure but negatively correlated with white blood cells and CRP. Interestingly, Xi et al[8] reported that the level of APN in patients with acute exacerbation of

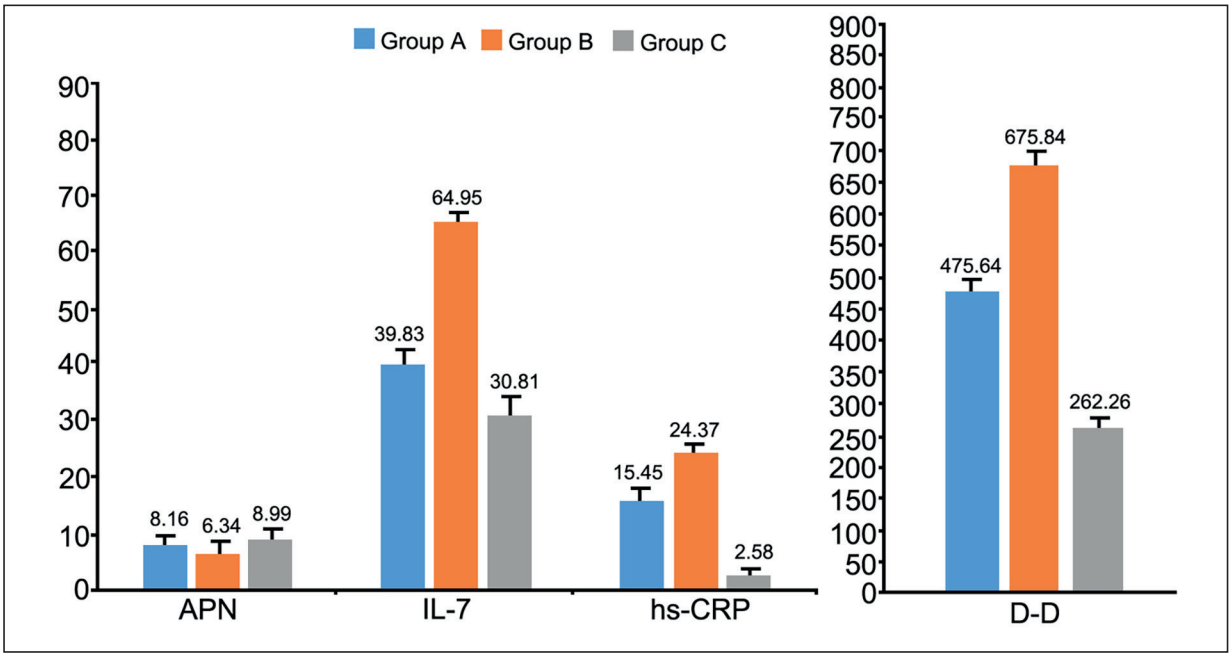

Figure 1. Expression levels of APN, IL-17, D-D, and hs-CRP in the three groups.

Table III. ROC analysis on APN, IL-17, D-D, and hs-CRP between patients with stable COPD and with acute exacerbation of COPD.

Variable	*p*-value	AUC	Sensitivity	Specitivity
APN	< 0.05	0.821	0.882	0.530
IL-17	< 0.05	0.802	0.834	0.560
D-D	< 0.05	0.758	0.841	0.480
hs-CRP	< 0.05	0.885	0.909	0.627

COPD was higher than that of patients with stable COPD. The reasons for the inconsistency might be due to the different exclusion and inclusion criteria, measurements of APN, duration length of acute exacerbation or respiration rates[9-11].

IL-17 can efficiently induce the expression of airway mucin 5AC and 5B in airway epithelial cells[12,13]. IL-17 is closely related with patients with airway smooth muscle cell proliferation in patients with COPD and can stimulate the secretion of IL-6 and TNF-α. It further leads to hyperplasia of fibrous connective tissue and airway smooth muscle which severely affects airway remodeling. This study found that levels of IL-17 from patients with acute exacerbation of COPD was significantly elevated compared to that of patients with stable COPD, indicating that IL-17 played a very important role in the development of partially reversible airflow limitation and inhibition of IL-17 can be used to optimize treatment regimen. It has also been reported that IL-17 has an inhibitory effect on neutrophils-induced inflammation in patients with COPD[14].

The previous finding[15] showed that there were prothrombotic and hypercoagulable states before acute exacerbation of COPD. Results from this study showed that the level of D-D from patients with acute exacerbation of COPD was significantly elevated compared to that of patients with stable COP. We proposed that the lack of oxygen in patients with acute exacerbation of COPD led to endothelial damage, increased tissue plasminogen activator secretion and coagulation factors consumption. At the same time, the patients' plasma fibrinogen was significantly increased and the fibrinolytic system functioned abnormally, leading to the increase of plasma D-D levels. These results suggest that, when the level of D-D is aberrantly increased, heparin therapy is of great significance for the prevention of disease progression.

hs-CRP is synthesized by the hepatocytes and released into the blood to stimulate the production of biologically active substances (e.g., endothelin-1, IL-6, etc.) in patients with COPD. It further enhances the inflammatory reaction. Levels of hs-CRP increase rapidly with inflammation or trauma but reduced quickly if inflammation or trauma is effectively controlled[16]. The level of hs-CRP thus can be applied for the monitoring of patient's inflammatory response without interference by treatment[17]. Our research showed that levels of hs-CRP from patients with acute exacerbation of COPD was significantly elevated compared to that of patients with stable COP. Consistently, Farrah et al[18] showed that after treatment, levels of procalcitonin, hs-CRP, and D-D were significantly decreased in patients with acute exacerbation of COPD. Our finding indicates that the combined use of biomarkers including APN, IL-17, D-D, and hs-CRP facilitates the diagnosis of acute exacerbation of COPD, although in-depth evaluation with a large amount of samples ought to be conducted in the future[22].

Table IV. Correlation between APN and IL -17, D-D, and hs-CRP.

Parameter	R (acute exacerbation)	*p* (acute exacerbation)	R (stable)	*p* (stable)	R (controls)	*p* (controls)
IL-17	-0.623	0.000	-0.399	0.000	-0.318	0.000
D-D	-0.375	0.000	-0.416	0.000	-0.663	0.000
hs-CRP	-0.382	0.000	-0.335	0.000	-0.292	0.000

Conclusions

We demonstrated that the level of APN was significantly decreased in patients with acute exacerbation of COPD, with an increase of IL-17, D-D, and hs-CRP. Levels of APN, IL-17, D-D, and hs-CRP are closely related with the stage of COPD and can be used as indicators to evaluate the severity of COPD in clinic.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Li YX, Zheng ZG, Liu N, Wang XN, Wu LL, Chen RC. [Risk factors for pulmonary embolism in acute exacerbation of chronic obstructive pulmonary disease]. Zhonghua Jie He He Hu Xi Za Zhi 2016; 39: 298-303.
2) Lee JY, Chon GR, Rhee CK, Kim DK, Yoon HK, Lee JH, Yoo KH, Lee SH, Lee SY, Kim TE, Kim TH, Park YB, Hwang YI, Kim YS, Jung KS. Characteristics of patients with chronic obstructive pulmonary disease at the first visit to a pulmonary medical center in Korea: The KOrea COpd Subgroup Study Team Cohort. J Korean Med Sci 2016; 31: 553-560.
3) Tang Q, Qin G. [Therapeutic effect of long-term noninvasive positive pressure ventilation on stable chronic obstructive pulmonary disease: a systematic review]. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2016; 41: 319-327.
4) Lopez-Campos JL, Abad Arranz M, Calero-Acuna C, Romero-Valero F, Ayerbe-Garcia R, Hidalgo-Molina A, Aguilar-Perez-Grovas RI, Garcia-Gil F, Casas-Maldonado F, Caballero-Ballesteros L, Sanchez-Palop M, Perez-Tejero D, Segado A, Calvo-Bonachera J, Hernandez-Sierra B, Domenech A, Arroyo-Varela M, Gonzalez-Vargas F, Cruz-Rueda JJ. Guideline adherence in outpatient clinics for chronic obstructive pulmonary disease: results from a clinical audit. PLoS One 2016; 11: e0151896.
5) Lee YM. Chronic obstructive pulmonary disease: respiratory review of 2014. Tuberc Respir Dis (Seoul) 2014; 77: 155-160.
6) Khetarpal R, Bali K, Chatrath V, Bansal D. Anesthetic considerations in the patients of chronic obstructive pulmonary disease undergoing laparoscopic surgeries. Anesth Essays Res 2016; 10: 7-12.
7) Singh A, Kumar S, Mishra AK, Kumar M, Kant S, Verma SK, Kushwaha RA, Garg R. Correlation between clinical characteristics, spirometric indices and high resolution computed tomography findings in patients of chronic obstructive pulmonary disease. Lung India 2016; 33: 42-48.
8) Kankaanranta H, Harju T, Kilpelainen M, Mazur W, Lehto JT, Katajisto M, Peisa T, Meinander T, Lehtimaki L. Diagnosis and pharmacotherapy of stable chronic obstructive pulmonary disease: the finnish guidelines. Basic Clin Pharmacol Toxicol 2015; 116: 291-307.
9) Park J, Song JH, Park DA, Lee JS, Lee SD, Oh YM. Systematic review and meta-analysis of pulmonary hypertension specific therapy for exercise capacity in chronic obstructive pulmonary disease. J Korean Med Sci 2013; 28: 1200-1206.
10) Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigare R, Dekhuijzen PN, Franssen F, Gayan-Ramirez G, Gea J, Gosker HR, Gosselink R, Hayot M, Hussain SN, Janssens W, Polkey MI, Roca J, Saey D, Schols AM, Spruit MA, Steiner M, Taivassalo T, Troosters T, Vogiatzis I, Wagner PD, COPD AEAHCoLMDi. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014; 189: e15-62.
11) Gea J, Pascual S, Casadevall C, Orozco-Levi M, Barreiro E. Muscle dysfunction in chronic obstructive pulmonary disease: update on causes and biological findings. J Thorac Dis 2015; 7: E418-438.
12) Vijayan VK. Chronic obstructive pulmonary disease. Indian J Med Res 2013; 137: 251-269.
13) Gupta D, Agarwal R, Aggarwal AN, Maturu VN, Dhooria S, Prasad KT, Sehgal IS, Yenge LB, Jindal A, Singh N, Ghoshal AG, Khilnani GC, Samaria JK, Gaur SN, Behera D, Group SKJftCGW. Guidelines for diagnosis and management of chronic obstructive pulmonary disease: Joint ICS/NCCP (I) recommendations. Lung India 2013; 30: 228-267.
14) Qureshi H, Sharafkhaneh A, Hanania NA. Chronic obstructive pulmonary disease exacerbations: latest evidence and clinical implications. Ther Adv Chronic Dis 2014; 5: 212-227.
15) Kim DK, Cho MH, Hersh CP, Lomas DA, Miller BE, Kong X, Bakke P, Gulsvik A, Agusti A, Wouters E, Celli B, Coxson H, Vestbo J, MacNee W, Yates JC, Rennard S, Litonjua A, Qiu W, Beaty TH, Crapo JD, Riley JH, Tal-Singer R, Silverman EK, Eclipse I, Investigators CO. Genome-wide association analysis of blood biomarkers in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012; 186: 1238-1247.
16) Kizer JR, Benkeser D, Arnold AM, Djousse L, Zieman SJ, Mukamal KJ, Tracy RP, Mantzoros CS, Siscovick DS, Gottdiener JS, Ix JH. Total and high-molecular-weight adiponectin and risk of coronary heart disease and ischemic stroke in older adults. J Clin Endocrinol Metab 2013; 98: 255-263.
17) Yaghootkar H, Lamina C, Scott RA, Dastani Z, Hivert MF, Warren LL, Stancakova A, Buxbaum SG, Lyytikainen LP, Henneman P, Wu Y, Cheung CY, Pankow JS, Jackson AU, Gustafsson S, Zhao JH, Ballantyne CM, Xie W, Bergman RN, Boehnke M, el Bouazzaoui F, Collins FS, Dunn SH, Dupuis J, Forouhi NG, Gillson C, Hattersley AT, Hong J, Kahonen M, Kuusisto J, Kedenko L, Kronenberg F, Doria A, As-

simes TL, Ferrannini E, Hansen T, Hao K, Haring H, Knowles JW, Lindgren CM, Nolan JJ, Paananen J, Pedersen O, Quertermous T, Smith U, Consortium G, Consortium R, Lehtimaki T, Liu CT, Loos RJ, McCarthy MI, Morris AD, Vasan RS, Spector TD, Teslovich TM, Tuomilehto J, van Dijk KW, Viikari JS, Zhu N, Langenberg C, Ingelsson E, Semple RK, Sinaiko AR, Palmer CN, Walker M, Lam KS, Paulweber B, Mohlke KL, van Duijn C, Raitakari OT, Bidulescu A, Wareham NJ, Laakso M, Waterworth DM, Lawlor DA, Meigs JB, Richards JB, Frayling TM. Mendelian randomization studies do not support a causal role for reduced circulating adiponectin levels in insulin resistance and type 2 diabetes. Diabetes 2013; 62: 3589-3598.

18) Kheradmand F, Shan M, Xu C, Corry DB. Autoimmunity in chronic obstructive pulmonary disease: clinical and experimental evidence. Expert Rev Clin Immunol 2012; 8: 285-292.

19) Gasse P, Riteau N, Vacher R, Michel ML, Fautrel A, di Padova F, Fick L, Charron S, Lagente V, Eberl G, Le Bert M, Quesniaux VF, Huaux F, Leite-de-Moraes M, Ryffel B, Couillin I. IL-1 and IL-23 mediate early IL-17A production in pulmonary inflammation leading to late fibrosis. PLoS One 2011; 6: e23185.

20) Durheim MT, Smith PJ, Babyak MA, Mabe SK, Martinu T, Welty-Wolf KE, Emery CF, Palmer SM, Blumenthal JA. Six-minute-walk distance and accelerometry predict outcomes in chronic obstructive pulmonary disease independent of Global Initiative for Chronic Obstructive Lung Disease 2011 Group. Ann Am Thorac Soc 2015; 12: 349-356.

21) Shin TR, Oh YM, Park JH, Lee KS, Oh S, Kang DR, Sheen S, Seo JB, Yoo KH, Lee JH, Kim TH, Lim SY, Yoon HI, Rhee CK, Choe KH, Lee JS, Lee SD. The prognostic value of residual volume/total lung capacity in patients with chronic obstructive pulmonary disease. J Korean Med Sci 2015; 30: 1459-1465.

22) Paone G, Leone V, Conti V, De Marchis L, Ialleni E, Graziani C, Salducci M, Ramaccia M, Munafo G. Blood and sputum biomarkers in COPD and asthma: a review. Eur Rev Med Pharmacol Sci 2016; 20: 698-708.