EXPRESSIONS OF SRAGE AND MMP-9 IN THE SERUM OF PATIENTS WITH COPD COMPLICATED WITH DIABETES MELLITUS AND CLINICAL SIGNIFICANCE

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ABSTRACT

Objective: *The aims of this study were to investigate the expressions and clinical features of advanced soluble glycation end products (sRAGE) and matrix metalloproteinases (MMPs)-9 in the serum of patients with chronic obstructive pulmonary disease (COPD) complicated with diabetes mellitus (DM).*

Materials and methods: *Seventy-six patients with COPD admited from January 2017 to November 2017 were divided into the observation group (O, patients with COPD-DM) and the control group (C, patients with COPD while non-DM). The patients were examined the pulmonary function, CAT score, and chest high-resolution computed tomography (HRCT) due to acute episodes (which is divided into the emphysema phenotype (Group OE) and airway inflammation phenotype (Group OA). Fasting blood was taken for routine examination and determination of sRAGE and MMP-9 levels.*

Results: *The expression level of sRAGE in Group O was 1414.64 pg/mL higher than that group C (937.98 pg/mL) (P<0.05). The sRAGE level in Group OA was 1868.63pg/mL higher than Group OE 1291.11 pg/mL (Z=-2.51, P=0.012). The sRAGE level in Group OA was was 1688.63pg/mL higher than Group C 1176.47 pg/mL (Z=-3.46, P=0.001); The serum sRAGE and MMP-9 levels were significantly correlated with the neutrophil percentage in group OA (r=0.73, 0.47, P=0.017, 0.014).*

Conclusions: *sRAGE and MMP-9 are involved in the pathogenesis of COPD combined with diabetes and have certain clinical value in evaluating clinical subgroup.*

Keywords: *COPD, Diabetes mellitus, sRAGE, MMP-9, HRCT.*

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by repeated airway inflammation caused by persistent respiratory symptoms and airflow limitation[(1)], resulting in destruction of lung structure and airway remodeling. COPD is also a heterogeneous disease. Even with similar airflow limitation, the clinical and imaging manifestations of COPD patients are varied from each other[(2)]. In addition to the scores of CAT (COPD assessment test), pulmonary function and the times of acute exacerbations, various complications are also important factors to worse the quality of life of COPD patients, leading to increased hospitalization and medical costs. One of the pathological characteristics of COPD is the destruction of the extracellular matrix of the lung[(3)]. Many inflammatory mediators, such as matrix metalloproteinases (MMPs), was involved in the destruction of extracellular matrix[(4)], which played a central role in lung remodeling of COPD. MMP-9 is an important member of the matrix metalloproteinases family, which participates in the pathogenesis of emphysema and is related to the severity of COPD[(5)]. Divo's study[(6)] has shown that MMP-9 is also involved in the pathogenesis

of many complications, especially with COPD specific comorbidity test (COTE), and further studies have shown that MMP-9 is also involved in the pathogenesis of diabetes[7]. The quality of life, the degree of acute exacerbation, the length of hospital stay and the overall cost of COPD patients were related with the complications. At present, there are many studies on COPD with hypertension, coronary atherosclerosis, and heart disease; while there were few studies on COPD with diabetes. Few studies have shown that COPD and diabetes are risk factors for each other since hyperglycemia caused some damage to lung function, which also plays an important role in the deterioration of COPD and mortality[8]. The common pathogenesis of COPD and diabetes includes oxidative stress and inflammation and many inflammatory mediators are involved in that. sRAGE is an isomer of receptor for advanced glycation end products (RAGE). RAGE binds with ligands to regulate inflammation signal transduction and mediate tissue damage[9]. As a protective factor of inflammation, sRAGE competes with RAGE to neutralize inflammatory ligand-mediated injury. Studies have shown that the expression of sRAGE was low in COPD wihle was very high in diabetes[10]. Whether the expression of sRAGE in COPD patients with diabetes needs further clinical research.

This study mainly studied the expression level of sRAGE and MMP-9 in COPD patients with diabetes and define the correlation of clinical features such as CAT score, times of acute exacerbation, high-resolution computed tomography (HRCT) phenotype[11, 12], which would helpful to find the pathogenesis of COPD patients with diabetes, including the inflammatory mediators, for individualized evaluation and treatment.

Materials and methods

Subjects

General information

From January 2017 to November 2017, a total of 76 patients with acute exacerbation of COPD were admitted to the Department of Respiratory Medicine, College of Petroleum Clinical Medicine, Hebei Medical University, including 49 males and 27 females, with the average age as 68.5±8.5 years. The patients were divided into two groups according to the presence or absence of diabetes. Group O consisted of 28 patients, including 21 males and 7 females, with the average age as 68.93±8.86 years. Group C consisted of 48 patients, including 28 males and 20 females, with the average age as 68.29±8.37 years. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Heibei Medical University.

Enrollment criteria

• Diagnostic criteria of COPD: according to GOLD 2017, patients' lung function was divided into Grade 1~4 according to the severity of airflow limitation. According to the symptoms and acute exacerbation, the patients were divided into Group A-D;

• DM: According to diagnostic criteria of DM by ADA[13];

• The patients and their families volunteered to participate in the study and signed the informed consent.

Exclusion criteria

• Thoracic deformity;

• With history of chest trauma, and/or history of surgery;

• History of mental illness;

• Acute myocardial infarction;

• Chronic renal insufficiency due to any cause;

• Advanced malignancy;

• Severe mental illness or cognitive impairment;

• Unwilling to participate in this study.

Collection of relevant indicators

Demographic data, laboratory tests, medical history data, and drug use. The number of patients' smoking years was also recorded. The HRCT phenotype, stable period, and CAT score in the latest acute exacerbation, first-time acute exacerbation, and number of acute exacerbations in the past 1 year were recorded.

Chest CT

Chest CT scanning method

All the patients were performed chest CT inspection (Siemens second-generation spiral CT Syngo CT, workplace 3D image processing software), target scanning parameters: scanning layer thickness 1 mm, layer spacing 0.5 mm, Sharp-Y algorithm, and matrix rebuild 1024×1024.

Image processing

The CT measurement indexes included the emphysema/bronchial wall thickness and the

diameter of parallel pulmonary artery in the same layer.

• Quantitative measurement of emphysema by visual subjective semi-quantitative method: the 1-mm-in-thickness thin layer CT image was transferred to the Syngo CT workplace 3D image processing software, with <-950HU being set as low-attenuation area (LAA). The measurements were then made at three anatomical levels (1 cm close to the upper edge of the aortic arch, 1 cm below the level of the carina, and 3 cm above the right side). The LAA score of each level was calculated based on the ratio of LAA to the lung field at each level[12, 14].

• Reconstruction of the right upper lobe apical bronchus by multiplanar recombination. After two experienced radiologists found the cross-section perpendicular to the long axis of the fifth bronchial lumen, the image was magnified by 2.5 times to measure the bronchial wall thickness (T) and the associated pulmonary artery diameter (PA); the ratio of T to PA was then calculated (T/PA).

Image classification

According to each patient's emphysema, T, and PA in the same layer, the above classification criteria were used to divide COPD patients into two phenotypes: the airway inflammation type (without emphysema or with mild emphysema, LAA≤1, with or without bronchial wall thickening, 29 cases) and the emphysema type (with emphysema, LAA≥2, with or without bronchial wall thickening, 47 cases), among which the bronchitis type of the observation group was abbreviated as OA, and the emphysema type was abbreviated as OE; the bronchitis type of the control group was abbreviated as CA, and the emphysema type was abbreviated as CE.

Detection of serum sRAGE and MMP-9

Collection of blood specimens

All the patients were sampled 3 ml of fasting elbow median venous blood at 8 am in the hospital within 24 hours of admission, which was then allowed to stand at room temperature for 1-2 hours. After the supernatant was precipitated, the sample was centrifuged at 3000 r/min for 10 min and sampled two copies of 200 μl of the supernatant placing in an EP tube and storing at -80°C for testing.

sRAGE and MMP-9 detection methods

The serum sRAGE and MMP-9 levels were determined by ELISA (RT-6000 enzyme labeling analyzer, Shenzhen Leidu Life Science Co., Ltd.) strictly according to the kit instructions (the sRAGE kit was purchased from Shanghai Research Institute Biotechnology Co., Ltd., and the MMP-9 kit was purchased from Beijing Dongge Biotechnology Co., Ltd.).

Statistical methods

Data analysis was performed using SPSS 23.0 software (SPSS Company, Chicago, Illinois, USA). Normality and homogeneity of the variance were tested before the analysis of measurement data (the normality was determined by the Shapiro-Wilk and P-P diagrams). The measurement data conforming to the normal distribution were represented by ($\bar{x}\pm s$) D and compared by the t test between groups and ANOVA among multiple groups.

The measurement data with non-normal distribution were represented by M (QR) and compared by the Mann-Whitney U test. Paired t-test was performed on the paired samples. Univariate correlation analysis was performed using the Pearson and Spearman correlation analysis. The chi-square test was used to compare the count data, with $P<0.05$ being considered as statistical significance.

Results

General information

This study totally enrolled 76 patients with COPD, with an average age as 68.5±8.5 years, including 49 males and 27 females. There were 56 smokers and 20 non-smokers. 28 patients were complicated with diabetes while 48 patients were not complicated with diabetes. According to HRCT, 47 patients were determined as the emphysema phenotype and 29 patients were determined as the airway inflammation phenotype. The CAT score of the patients with stable COPD was 12.30±5.24, and the CAT score of the patients with acute exacerbation was 20.63±4.63 (Table 1).

Variable	Value	Ratio
Number	76	-
Age (years)	68.5±8.5	-
Gender: M/F	49/27	64%/36%
Smoking (yes/no)	56/20	74%/26%
Combined with diabetes (yes/no)	28/48	37%/63%
Emphysema phenotype(OE/CE)	17/30	22%/40%
Airway inflammation phenotype(OA/CA)	11/18	14%/24%
Stable CAT score	12.30±5.24	-
CAT score in acute exacerbation stage	20.63±4.63	-

Table 1: COPD patients characteristics.
Date are presented as mean±SD and n (%).

Analysis of Age, gender, and smoking

The median age of group O (68.93±8.86) showed no statistical significance than that of group C (68.29±8.37) (P>0.05), as well as the gender and the proportion of smokers (P>0.05). There was no statistical significance in the number of cigarettes per year between-group O (30 packs per year, 20-40) and group C (30 packs per year, 20-42.5) (P>0.05).

Analysis of routine inflammation media in the peripheral blood

The proportion of neutrophils in group O was 76.78±10.72% and significantly higher than group C (n=-2.01, P=0.048). The platelet count in group O was (193.96±56.44)×10^9/L and significantly lower than group C (230.35±84.53)×10^9/L (P=0.03). the C-reactive protein in group O was 5.6(3.63-20.00) mg/L and significantly lower than group C 25 (7.6-52.71) mg/L (Z=-3.59, P<0.001), the Fasting plasma glucose (FPG) of the group O was higher than group C (7.32±2.21 mmol/L vs. 5.36±1.11 mmol/L, t=10.81, P<0.05, Table 2).

Comparison of life quality score and number of acute exacerbation

In group O, the stable CAT score was (13.11±4.07 points), the CAT score in acute exacerbation was (20.82±4.48 points), and the number of acute exacerbations in the past 1 year was (1(1-2), which showed no statistical significance to group C (11.83±5.35 points), (20.52±4.97 points), and (1(0-2) times) (P>0.05). The CAT score in group O was negatively correlated with FEV1% pred (r=-0.67, P<0.001). The CAT score in group C had no correlation with FEV1% pred (P>0.05).

Comparison of HRCT phenotype and lung function

The comparison of the ratio of airway inflammation phenotype and emphysema phenotype between the two groups showed no statistical significance (X^2=0.03, P=0.877).

Group OBS had 17 OE cases and 11 OA cases, and Group CON had 30 CE cases and 18 CA cases. There was no statistical significance in FEV1%

	Group O	Group C	T, X^2or Z	*P*
Number	28	48		
Age	68.93±8.86	68.29±8.37	t=0.31	0.76
Gender: M/F	21/7	28/20	X^2=2.15	0.14
Smoking (yes/no)	23/5	33/15	X^2=1.64	0.2
Cigarettes per year	30(20-40)	30(20-42.5)	Z=-0.65	0.516
Percentage of neutrophils	76.78±10.72*	71.08±12.61	t=-2.01	0.048
Percentage oflymphocytes	15.91±8.86	19.10±10.55	t=1.35	0.18
Platelet	193.96±56.44*	230.35±84.53	t=2.25	0.03
C-reactive protein	5.6(3.63-20.00)*	25(7.6-52.71)	Z=-3.59	<0.001
FPG (mmol/L)	7.32±2.21*	5.36±1.11	t=10.81	0.043
Stable CAT score	13.11±4.07	11.83±5.35	t=-1.02	0.31
CAT score in acute exacerbation stage	20.82±4.48	20.52±4.97	t=-0.27	0.79
Number of acute exacerbation in the past year	1(1-2)	1(0-2)	Z=-1.60	0.11
First-time acute exacerbation(months)	8.5(3-12)	12(5-16.75)	Z=-1.35	0.176
HRCT phenotype (emphysema phenotype/airway inflammation phenotype)	17/11	30/18	X2=0.03	0.877
LAA score	9.00±4.09	9.61±4.23	t=0.01	0.98
FVC%	52.78±16.65	52.63±16.58	t=-0.04	0.97
FEV1%	36.28±15.44	40.21±16.45	t=1.03	0.31
sRAGE	1415.64(1279.91-1692.2)*	937.98(806.06-1269.16)	Z=-3.14	0.002
MMP-9	132.42(122.21-144.43)	129.29(121.70-137.90)	Z=-0.71	0.48
Administration of ACEI or Statins (yes/no)	14/14	16/32	X^2=2.06	0.15
Non-invasive ventilation (yes/no)	4/24	11/37	X^2=0.83	0.36
Glucocorticoids generally or aerosol inhalation glucocorticoids (yes/no)	27/1	41/7*	t=11.95	0.001

Table 2: Comparison of sRAGE and MMP-9 levels and clinical data in two COPD groups.
**Compared with the control group, P<0.05.*

pred (36.28±15.44)% between-group O and group C (40.21±16.45)% (P=0.31).

Serum levels of sRAGE and MMP-9

The serum level of sRAGE in group O was 1415.64(1279.91-1692.2) pg/mL and significantly higher than group C 937.98(806.06-1269.16) pg/mL (P=0.001). There was no statistical significance in the serum level of MMP-9 between-group O (132.42, 122.21-144.43 ng/mL) and group C (129.29, 121.7-137.9 ng/mL, P=0.427, Table 2).

Comparison of other clinical indicators

There was no statistical significance in the proportion of using ACEI and Statin between the two groups (P=0.15). There was no statistical significance in the proportion of non-invasive ventilation between the two groups (P=0.36). 68 patients in 76 cases (89.47%) used glucocorticoids generally or aerosol inhalation glucocorticoids. In group O, there were 41 patients (53.95%) use glucocorticoids generally and 7 patients (9.21%) did not use; in group C, there were 27 patients (35.52%) used glucocorticoids generally and 1 patient (1.32%) did not use glucocorticoid.

Correlation between serum sRAGE/MMP-9 and clinical features

Serum sRAGE was positively correlated with the percentage of neutrophils (r=0.47, P=0.014) while negatively correlated with the percentage of lymphocytes (r=-0.54, P=0.004) in group O. Serum MMP-9 showed no correlation with the percentage of neutrophils nor the percentage of lymphocytes (P>0.05) in group O. There was no correlation between serum sRAGE and MMP-9 (r=0.11, P=0.59) in group O. There was no correlation between serum sRAGE/MMP-9 and the percentage of neutrophils nor lymphocytes in group C (P>0.05).

There was no correlation between serum sRAGE/MMP-9 and stable CAT score, number of acute exacerbation in the past 1 year, or FEV1% pred in group O or group C (P>0.05, Table 3).

Expression and correlation of serum sRAGE and MMP-9 in HRCT phenotypes

The expression level of sRAGE in group OA (1688.63(1342.42-2099.14) pg/mL) was higher than group CA (1176.47(850.26-1322.31) pg/mL), and the difference was statistically significant (Z=-3.46, P=0.001); the expression level of sRAGE in group OE (1290.11(800.77-1614.65) pg/mL) was higher than group C E (896.8(743.62-1268.23) pg/mL), but the difference was not statistically significant (Z=-1.41, P=0.16). Comparison of MMP-9 between-group OA and group OE. The comparison of MMP-9 levels in group OA, OE (135.18(113.92-142.72), 131.361(26.68-152.09) ng/mL), and group CA, CE (125.72(119.42-131.98), 133.28(123.25-142.49) ng/mL) showed no statistical significance (Z=-0.59, -0.29, P=0.56, 0.77). The expression level of sRAGE in group OA (1688.63(1342.42-2099.14) pg/mL) was higher than group OE (1290.11(800.77-1614.65) pg/mL), and the difference was statistically significant (Z=-2.51, P=0.012). The sRAGE expression level in group CA (1176.47(850.26-1322.31) pg/mL) was higher than group CE (896.8(743.62-1268.23) pg/mL), but the difference was not statistically significant (Z=-1.10, P=0.27). The expression level of MMP-9 in group OA (135.18(113.92-142.72) ng/mL) was not statistically different from that in group OE (131.36(126.68-152.09) ng/mL), (Z=-0.73, P=0.47). The expression level of MMP-9 in group CA (133.28(123.25-142.49) ng/mL) was lower than group CE (125.72(119.42-131.98) ng/mL), and the difference was statistically significant (Z=-2.11, P=0.035). The expression level of serum sRAGE was significantly correlated with the serum MMP-9 expression level in group OA (r=0.73, P=0.017, Figure 1), but there was no such correlation in group C (r=0.02, P=0.96). There was no correlation between the expression levels of sRAGE and MMP-9 in group OE nor group CE (r=-0.22, -0.29, P>0.05). The expression level of sRAGE was correlated with the LAA negatively in group O (r=-0.399, P=0.029) while no such correlation was found in group C (r=0.123, P=0.399, Figure 2).

Clinical data		Group O		Group C	
		r	*P*	r	*P*
	MMP-9	0.11	0.59	-0.286	0.06
	Percentage of neutrophils	0.47	0.014*	0.008	0.957
	Percentage of lymphocytes	-0.54	0.004*	-0.042	0.787
sRAGE	Stable CAT score	0.20	0.33	0.139	0.369
	CAT score in acute exacerbation stage	0.19	0.32	0.14	0.331
	Number of acute exacerbation in the past year	0.16	0.433	0.071	0.649
	FEV1% pred	-0.20	0.308	0.199	0.196
	Percentage of neutrophils	-0.10	0.637	0.251	0.086
	Percentage of lymphocytes	0.083	0.676	-0.207	0.158
MMP-9	Stable CAT score	-0.103	0.603	-0.044	0.767
	Number of acute exacerbation in the past year	0.066	0.739	0.134	0.363
	FEV1% pred	0.129	0.511	-0.019	0.897

Table 3: Correlation between sRAGE, MMP-9 and clinical data in the two COPD groups.
**The association between sRAGE and other data, P< 0.05.*

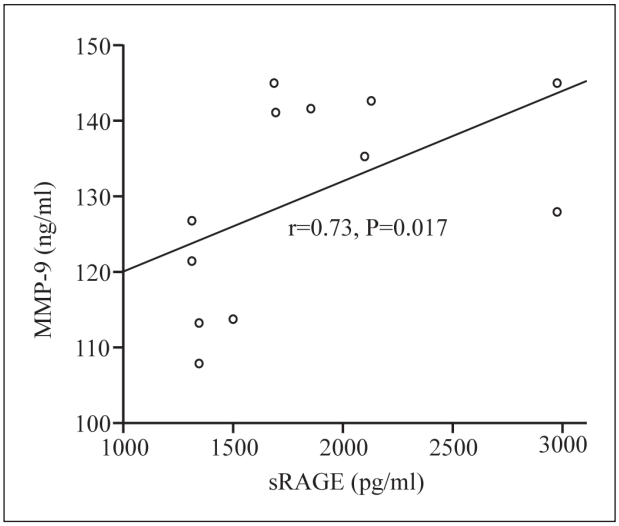

Figure 1: The correlation between sRAGE and MMP-9 of the airway inflammatory phenotype in the observation group.

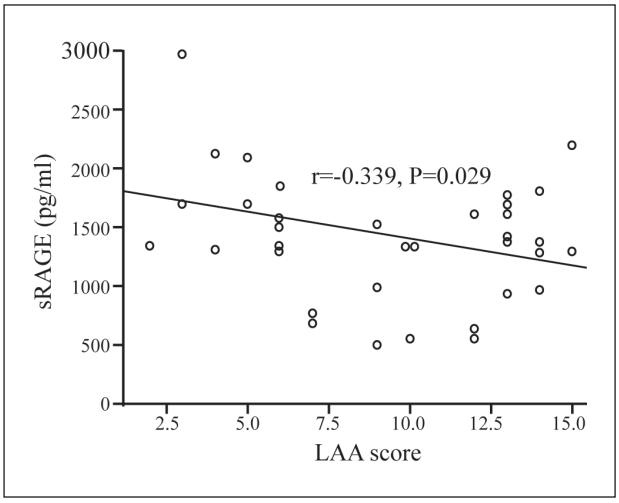

Figure 2: The level of sRAGE was correlated with the LAA negatively in group observation group.

Discussion

The main results of the study: Vanfleteren et al.[15] showed that 97.7% of COPD patients had one or more complications, which could lead to more severe acute onset of COPD, resulting in higher hospitalization, mortalityandcosts. Studies have shown that diabetes is one of the common complications of COPD, which increases hospitalization time and mortality in patients with acute COPD attacks. In this study, 37% of COPD patients complicated with diabetes. Since there are relatively few studies on the clinical heterogeneity of these patients, this study mainly explores the expression levels of sRAGE and MMP-9 in COPD patients with diabetes to find the correlation between clinical subtypes and clinical evaluation of COPD patients with diabetes. We have found that the expression of sRAGE in COPD patients with diabetes is higher than without; the sRAGE expression is related to the type of lung structural damage, the expression level of sRAGE in COPD with diabetes was higher than that in emphysema and the expression of airway inflammation phenotype sRAGE in COPD patients with diabetes was higher than that in without. Meanwhile, the sRAGE expression level was correlated with LAA in diabetes with COPD. We've also found the serum sRAGE and MMP-9 in airway inflammation type were related to the percentage of neutrophils; Serum levels of sRAGE and MMP-9 were not correlated with CAT scores and times of acute exacerbation.

Correlation between COPD and DM

Multiple studies have shown that COPD and DM are mutually risk factors and chronic systemic inflammation may be one of the common pathogenesis between COPD and DM[16]. Chronic inflammation induces the activation of the NF-kB pathway and the release of inflammatory mediators in the cells, thus leading to an increase in chronic blood glucose. Animal studies have shown that hyperglycemia on the respiratory system increases oxidative stress. Oxidative stress of hyperglycemia includes: increased glucose self-oxidation, increased activity of polyol pathway, increased activity of protease C, and decreased antioxidant clearance, as wellas non-enzymatic glycosylation of proteins, for example, collagen may finally form advanced glycation end products (AGEs) with prolonged saccharification time. Increased oxidative activity increases AGEs, induces the synthesis and cross-linking of collagens, and disrupts lung tissue structure and gas exchange obstacle[17]. In addition, pulmonary vascular microvascular diseases caused by diabetes, autonomic neuropathy of the lungs, and glycosylation may lead to decreased elastic retraction of the lung parenchyma which ultimately leads to decreased lung function.

In this study, FEV1% pred in patients of group O was lower than that in group C, but there was no statistical difference (P>0.05). The reason may be related to the fact that the decline of lung function is more related to various inflammation mediators, and the inflammatory mediators leading to DMpartially involves in the decline of lung function, so dynamic observation of pulmonary function in patients with COPD-DM is of far-reaching significance for clinical research.

Assessment value of CAT score toward patients with COPD-DM

The assessment of the severity of COPD is currently based on symptoms and acute exacerbation. The CAT score is a novel multidimensional metric scale that was developed by Jones in 2009 to assess the clinical symptoms of COPD patients[18, 19]. This scale is closely related to the health status of COPD patients, and in 2017, GOLD used the CAT score for the grouping of disease severity. A number of studies have found that the CAT score is significantly higher in the acute exacerbation stage of COPD than in the stable stage. The difference in the CAT score between the stable and acute exacerbation stages has been large, with an average improvement of 7 units. The higher the CAT score, the more significant association with the first-time acute exacerbation and worsening risks[20].

There has been no report on the life quality assessment of patients with COPD-DM using the CAT score. Certain literatureshave shown that patients with type 2 diabetes have more frequent dyspnea and chronic cough than the general population of the same age[21]. Hyperglycemia can damage the innate and adaptive immunity and inhibit the host's response to infection. Diabetes increases the potential of bacterial infections in the lungs in patients with COPD. Continuous hyperglycemia leads to poor COPD treatment, long hospital stay, and even death due to uncontrollable infection. In this study, the stable CAT score (13.11±4.07) in group O was significantly lower than that in the acute exacerbation stage (20.82±4.48), and the difference was about 7 units, indicating that DM is involved in the clinical course of COPD patients ot various degrees, and the mechanism is more complicated.

The CAT score can reflect the degree of systemic inflammatories to a certain extent. Some scholars have shown that there is a significant positive correlation between the CAT score and steroid and/or antibiotic treatment frequency. Hassan[22] once evaluated the baseline CAT scores of 105 patients with stable COPD, who were divided into 4 groups according to their individual CAT scores. The results showed that there was a correlation between the mean FEV1% and the mean CAT score in the four groups ($P<0.001$). In this study, the stable CAT score was positively correlated with the number of acute exacerbation in the past 1 year and negatively correlated with FEV1% pred. in the patients of group O, but in the patients of group C, the stable CAT score was positively correlated with the number of acute exacerbation in the past year while not associated with decreased lung function, indicating that the CAT score can predict the risk of future acute attacks. Poor glycemic control in diabetic patients increases the risk of infection in patients with COPD, but acute exacerbations of COPD patients are induced by a variety of factors. The decline in lung function in patients with COPD-DM is closely related to the CAT score, so community doctors or patients can predict acute exacerbation and pulmonary function by the CAT score.

Expression of serum sRAGE in patients with COPD-DM

One of the common pathogenesis of COPD and DM is oxidative stress plus inflammatory response. AGEs bind with their receptors (RAGE) to mediate inflammatory damage and play a role in the mechanism of diabetes. sRAGE is an isomer of RAGE, which acts as a "bait" to block the binding of AGEs and RAGE to protect the body from inflammatory damage. Several studies have shown that sRAGE can be used as a sRAGE in vivo protective factor, sRAGE can attenuate neutrophilic asthma by blocking the HMGB1/RAGE signaling in airway dendritic cells[23].

Multiple studies have shown that sRAGE is at a low level in the circulation of patients with COPD[24]. Smith et al[25] showed that the serum sRAGE in the patients with stable COPD was lower than that in healthy controls, and was even lower in the acute exacerbation stage. Furthermore, sRAGE was significantly associated with FEV1%. The lower the plasma sRAGE concentration, the higher the airflow obstruction. Sukkar found that the sRAGE level in patients with neutrophilic asthma or COPD was significantly lower than those without neutrophilia. Nakamura found that the sRAGE level in the circulation was elevated in diabetes. Basta found that serum sRAGE levels were higher in patients with type 1 and type 2 diabetes than that in healthy subjects, suggesting that endothelial cell damage may lead to increased RAGE cleavage, as well as elevated sRAGE level.

In this study, the serum sRAGE level in the patients with COPD-DM was significantly higher than those with COPD-non-DM ($P<0.05$). the serum sRAGE expression and neutrophil percentage in the patients of group O were significantly higher than group C, and serum sRAGE was positively correlated with neutrophil percentage in the patients of group O, indicating that the circulating sRAGE

is involved in the pathogenesis of COPD-DM, consistent with other reports. The results of this study suggest that inflammatory mediators, such as neutrophils, cause increased expression of RAGE in patients with COPD-DM, which thus leads to increased expression of sRAGE.

Previous studies have shown that many drugs may affect the sRAGE level, and in order to determine whether Statins can affect the sRAGE expression level, patients with untreated hypercholesterolemia and healthy controls applied Statin therapy for ≥3 months, followed by testing the plasma sRAGE level. It was found that the sRAGE level in patients with untreated hypercholesterolemia was lower than those in the other two groups. Forbes found that the plasma sRAGE level in the patients with type 1 diabetes who received treatment of angiotensin-converting enzyme inhibitor (ACEI) perindopril were significantly higher than those receiving placebo or nifedipine (calcium antagonist). Tang also reported that the dose of corticosteroids was positively correlated with the plasma level of logarithmic conversion of sRAGE[26]. Studies have shown that oral glucanose treatment with rosiglitazone can increase the circulating sRAGE level. There was no significant difference in the use of Statin or ACEI between the two groups in this study (P>0.05). The use of the above drugs showed no effect on the difference in the expression level of sRAGE between the two groups.

Expression of MMP-9 in patients with COPD-DM

MMPs are proteolytic enzymes that degrade matrix components, and MMP-9 is a zinc- and calcium-dependent proteolytic enzyme. By degrading the extracellular matrix and cell membrane, the alveolar cavity is enlarged and the elastic retraction force of the alveoli is weakened, resulting in gas retention. Furthermore, by activating inflammatory factors, destroying the epithelial or endothelial structure, participating in the inflammatory response of the airway and lung reconstruction, it may lead to the occurrence of emphysema in COPD[27].

Several studies have shown that MMP-9 is associated with the severity of COPD. Omachi also found that the plasma MMP-9 was negatively correlated with FVC and FEVI%, and positively correlated with peripheral blood leukocyte count. Studies have found that the polymorphism of MMP-9 (C-1562T) in patients with COPD is associated with emphysema in the upper lung. Other studies have found that MMP-9 is also associated with moderate lobular central emphysema and paraventricular emphysema. Some scholars have indicated that MMP-9 is involved in the pathogenesis of diabetes and diabetic complications such as diabetic retinopathy. MMP-9 has the ability to degrade insulin and is capable of activating IL-8, a major chemokine of neutrophils and monocytes, and MMP-9 disrupts the retinal basement membrane barrier by inflammatory cell migration.

The results of this study showed no statistical significance in the MMP-9 expression level between the two groups, suggesting that MMP-9 plays a role in the pathogenesis of COPD and is also involved in the inflammatory response of DM. however, whether MMP-9 is only partially involved in the pathogenesis of a certain link or a subtype of COPD-DM still needs further research.

Expressions and correlation of serum sRAGE and MMP-9 in HRCT phenotype

Studying HRCT phenotype is one of the hotspots of current COPD phenotype research. High-resolution lung CT can provide a macroscopic understanding of the degree of chronic airway inflammation and emphysema. Studies have shown that[28] COPD is divided into two CT phenotypes, the emphysema dominant type (≥35% emphysema, <1.75 mm bronchial wall thickness) and the airway dominant type (<35% emphysema, ≥1.75 mm bronchial wall thickness). Studies have shown differences in the inflammatory mediators and airflow limitations between different CT phenotypes. Milan also reported that COPD and diabetes can increase the risk of non-emphysema phenotype. Miniati has found that low levels of circulating sRAGE can be used as an independent predictor of emphysema in patients with COPD, and the lower the level of sRAGE, the higher the degree of emphysema[29].

After adjustment considering smoking history and comorbidities, the relationship is still statistically significant. Iwamoto and Sukkar[24, 30] also found that low levels of plasma sRAGE are associated with the severity of emphysema, and the plasma sRAGE level is independently associated with carbon monoxide diffusion. In the ECLIPSE study, the circulating sRAGE level is associated with the progression of emphysema after adjustment for potential confounders[28].

Although hyperglycemia in diabetic patients leads to endothelial cell damage, it also causes an increase in the RAGE cleavage, which leads to an

increase in the sRAGE level. The results of this study showed that the expression level of sRAGE in group OA was significantly higher than that in group CA (P<0.01), which fully indicated the involvement of DM in airway inflammation. The study also found that the expression of sRAGE in group OE was lower than that in group OA (P=0.012), indicating that even combined with diabetes, sRAGE is still involved in the pathogenesis of airflow limitation of emphysema-type COPD, consistent with other studies. Both in the observation group and in the control group, the ratio of sRAGE in the emphysema phenotype was lower than that in the bronchitistype, and the mechanism was unclear. Miniati has found that the lower the sRAGE level, the higher the degree of emphysema. Basa also believes that the endothelial cell damage causes increased RAGE cleavage in diabetic patients, thus resulting in elevated levels of sRAGE, which requires further studies targeting the extent of emphysema and the expression level of sRAGE.

Previous studies have found that the source of sRAGE can also be proteolytically cleaved by full-length RAGE via metalloproteinases ADAM10 and MMP9, leading to the release of sRAGE[31]. Moreover, MMP-9 is an important factor in airway remodeling in patients with COPD, and through activating inflammatory factors, it can disrupt epithelial or endothelial structures and participate in the airway and lung remodeling. In this study, the serum MMP-9 level in group OA was significantly correlated with the serum sRAGE expression level (r=0.73, P=0.017), suggesting that sRAGE and MMP-9 are involved in the pathogenesis of COPD-DM. In conclusion, the pathogenesis of COPD with diabetes is more complex. sRAGE and MMP-9 are involved in the pathogenesis of some inflammation, which was important for the evaluation of clinical subgroups. The limitation of this study includes more inflammatory mediators, such as IL-8, in the pathogenesis of COPD with diabetes mellitus and related studies, should be involved.

In conclusion, the pathogenesis of COPD combined with DM is more complicated. sRAGE and MMP-9 are involved in the pathogenesis of partial inflammation, and have certain clinical value for clinical subgroup evaluation.

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