CORRELATION BETWEEN SERUM SDC4 AND SEVERITY OF IDIOPATHIC INTERSTITIAL PNEUMONIA

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ABSTRACT

Objective: *To analyze the correlation between serum SDC4 and severity of idiopathic interstitial pneumonia (IIP).*

Methods: *From September 2018 to August 2019, 56 patients with IIP who were diagnosed and treated in our hospital for the first time were selected for the IIP group, 56 patients with nonspecific interstitial pneumonia were selected for the NSIP group, and 56 healthy people were selected for the normal control group. The levels of SDC4 in serum were measured by ELISA; FVC, FEV1, TLC, DLCO, and PaO2 were detected by a lung function instrument; HRCT scores were evaluated by the Muller method. The changes in serum SDC4 level, pulmonary function, and HRCT score were observed, and the correlation between serum SDC4 and HRCT score was analyzed.*

Results: *Compared with the normal control group, neutrophils and leukocytes in the NSIP group and the IIP group were significantly increased (P<0.05), and lymphocytes were significantly decreased (P<0.05). Neutrophils and leukocytes in the IIP group were significantly higher than those in the NSIP group (P<0.05), and lymphocytes were significantly lower than those in the NSIP group (P<0.05). SDC4 levels in the NSIP and IIP groups were higher than those in the normal control group. SDC4 levels in the IIP group were significantly higher than those in the NSIP group (P<0.05). The levels of FEV1 in the IIP and NSIP groups were significantly higher than in the normal control group (P<0.05), and the levels of FVC, TLC, DLCO, and PaO2 in the IIP group were significantly higher than in the NSIP group (P<0.05). The levels of FVC, TLC, DLCO, and PaO2 in the IIP group were significantly higher than in the NSIP group (P<0.05). In the NSIP group, SDC4 levels were significantly decreased (P<0.05); serum SDC4 levels were significantly positively correlated with FEV1 (P<0.05) and negatively correlated with FVC, TLC, DLCO, and PaO2 (P<0.05); serum SDC4 was positively correlated with HRCT score in the IIP and NSIP groups (P<0.05).*

Conclusion: *Serum SDC4 is closely related to the severity of IIP. Regular monitoring of SDC4 water serum concentration can determine the severity of lung interstitial damage.*

Keywords: *Idiopathic interstitial pneumonia, serum SDC4, disease severity, correlation.*

DOI: 10.19193/0393-6384_2022_1_55

Received *March 15, 2020;* ***Accepted*** *October 20, 2020*

Introduction

Idiopathic interstitial pneumonia (IIP) is a group of unexplained progressive lower respiratory diseases[(1)]. Clinically, it is also called idiopathic pulmonary interstitial fibrosis as it causes slowly progressing diffuse alveolitis and alveolar structural disorders. This leads to inflammation in multiple locations such as the pulmonary interstitium, the peripheral airways, the pulmonary small blood vessels, and the alveoli. Inflammation in the alveoli destroys their structure, thus leading to complete fibrosis in the alveolar cavity and vesicular honeycomb lung[(2)]. Studies by Deng Yuetong and others found that the incidence of lung cancer in IIP patients is significantly higher than that of the general population, with their main clinical feature being progressive dyspnea[(3)]. The clinical manifestations are fatigue, weight loss, joint pain, low-grade fever, and irritating dry cough with a

small amount of sticky sputum, as well as audible velcro rales and progressive hypoxemia in the lung base and underarm area. IIP patients can suffer complications such as pulmonary hypertension, right heart failure, and pulmonary heart disease due to pulmonary fibrosis, which can be life-threatening.

Syndecan-4 (SDC4) is mainly synthesized by endothelial cells and can also be found in vascular endothelial cells and smooth muscle cells, contributing to the anti-fibrotic process[4]. However, there are few research reports on links between serum SDC4 and the severity of illness in patients with IIP. This study aimed to explore the correlation between serum SDC4 and the severity of illness in patients with IIP.

Materials and methods

General information

This study was approved by the hospital ethics committee. 56 IIP patients diagnosed and treated in our hospital from September 2018 to August 2019 were selected for the IIP group, aged 42-63 years, including 32 males and 24 females.

Inclusion criteria for the IIP group were:

• Progressive dyspnea without clear cause; S

• Surgical biopsy showing that histology was consistent with ordinary interstitial pneumonia-like changes;

• Lung function examination showing restrictive ventilatory dysfunction with decreased diffusion function;

• Routine chest X-ray and high-resolution CT (HRCT) examinations of the chest showing diffuse shadows of reticular nodules or honeycombed lungs in both lower lungs and under the pleura.

For the NSIP group, 56 non-specific interstitial pneumonia (NSIP) patients who were treated in our hospital during the same period were selected, aged 41-62 years, consisting of 35 males and 21 females.

Inclusion criteria for the NSIP group were:

• Lung function test showing restrictive ventilatory disorder;

• Dyspnea, coughing;

• Diffuse reticular shadows of subpleural or double lungs were potentially detected by HRCT, but only if the subpleural lung tissue was not involved.

The diagnosis of patients in the IIP group and the NSIP group met the diagnostic criteria of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) for idiopathic interstitial pneumonia (2013 edition).

Finally, 56 healthy subjects were selected as the normal control group.

Exclusion criteria were:

• Age ≤18 years old or ≥80 years old;

• Person suffers from various acute and chronic infectious diseases or heart, kidney, or liver insufficiency;

• Women during pregnancy.

All patients or their families were informed about this study and signed an informed consent form. There was no statistically significant difference in basic data such as gender and age of patients between the three groups, and they were comparable (P>0.05).

Method

All research subjects were asked about their medical history in detail after admission, and researchers accurately recorded their basic information such as age, sex, height, weight, and whether they had hypertension.

Blood specimen collection

5 ml of fasting venous blood was drawn the morning after admission in each group. Samples were centrifuged at 3000 r/min for 10 minutes and the upper serum was collected and stored at -20 °C for testing.

Pulmonary function test

Arterial blood gas analysis was performed in all three groups, and oxygen partial pressure (PaO2%) was recorded. Forced vital capacity (FVC%), forced expiratory volume in the first second (FEV1%), total lung volume (TLC%), and carbon monoxide diffusion volume (DLCO) were measured. Bronchoalveolar lavage fluid (BALF) examination was performed, and the treatment was performed according to BALF cytology classification.

Observation indicators

• An enzyme-linked immunosorbent assay (ELISA) (Shanghai Enzyme Linked Biotechnology Co., Ltd.) was used to determine changes in serum SDC4 levels. All operations were carried out in strict accordance with the instrument and kit instructions.

• A pulmonary function tester (Beijing Zeao Medical Technology Co., Ltd., Japan Minor MINATO Pulmonary Function Tester AS-507) was used to detect the percentage of FVC, FEV1, TLC, DLCO, and PaO2 levels. The measurement standard takes the normal reference value of Chinese adult lung function as the normal prediction value.

• HRCT score: The Muller method was used to score HRCT for each group, and the ground-glass, grid-like, and honeycomb-like changes were scored respectively. For HRCT scoring criteria, see Table 1.

Lesion area	Scores
No lesions	0 point
Lesion area≤5%	1 point
Lesion area5~25%	2 points
Lesion area 25~50%	3 points
Lesion area 50~75%	4 points
Lesion area >75	5 points

Table 1: HRCT scoring standards.
Note: The total of the three change scores is HRCT score.

Statistical analysis

SPSS 14.0 statistical software was used for data statistics. Measurement data was represented as standard deviation ($\bar{x}\pm s$), enumeration data was represented as (n(%)).

The comparison between the normal control group and the patients in the IIP group and NSIP group used two independent samples t-tests. The correlation between each factor and the severity of the disease was analyzed by a Spearman correlation. The comparison between the data was statistically significant and expressed as P<0.05.

Results

Comparison of baseline data in three groups

Comparing the normal control group with the NSIP group and the IIP group, the three groups had no statistically significant differences in age, gender, smoking, diabetes, chronic heart failure, or coronary heart disease (P≥0.05), and they were comparable. Compared with the normal control group, the neutrophils and white blood cells of the NSIP group and the IIP group were significantly increased, but the IIP group levels were significantly higher than the NSIP group levels (P<0.05).

In the IIP and NSIP groups, lymphocytes were significantly reduced, and the IIP group lymphocyte count was significantly lower than that of the NSIP group (P<0.05); see Table 2.

Comparison of SDC4 levels in three groups

Compared with the normal control group, the SDC4 level of patients in the NSIP group and the IIP group was significantly higher, and the difference in the IIP group was significantly higher than that of the NSIP group (P<0.05). See Table 3.

Groups	Age	Male/Female	Smoking	Diabetes	Chronic	Coronary
Normal control	56.71±9.42	31/25	15	-	-	-
NSIP	56.89±9.53	35/21	21	8	13	9
IIP	56.31±9.11	32/24	29	7	14	11

Groups	Neutrophils	Lymphocytes	Leukocytes
Normal control	51.24 (49.88, 61.23)	19.66 (12.56, 29.66)	5.89 (4.69, 8.75)
NSIP	72.31 (62.18, 81.49)*	15.87 (9.44, 27.11)*	7.39 (5.48, 10.26)*
IIP	84.51 (75.87, 90.65)*#	8.65 (4.98, 13.75)*#	10.11 (6.78, 15.54)*#

Table 2: Comparative analysis of baseline data in the normal control group, NSIP group, and IIP group ($\bar{x}\pm s$).
*Note: *indicates P<0.05 compared with the normal control group, #indicates P<0.05 compared with the NSIP group.*

Groups	Cases	SDC4 (ng/ml)
Normal control	56	6.05±1.23
IIP group	56	10.20±4.32*#
NSIP group	56	8.03±3.23*

Table 3: Comparative analysis of SDC4 levels in the normal control group, NSIP group, and IIP group ($\bar{x}\pm s$).
*Note: *indicates P<0.05 compared with the normal control group, #indicates P<0.05 compared with the NSIP group.*

Comparison of lung function in three groups

Compared with the normal control group, the FEV1 value of patients in the IIP and NSIP groups was significantly increased, and the IIP group value was significantly higher than that of the NSIP group (P<0.05). The values of FVC, TLC, DLCO, and PaO2 were significantly reduced. However, the IIP group levels of these four measurements were significantly lower than the NSIP group levels; this difference was statistically significant (P<0.05). See Table 4.

Groups	FEV1 (%)	FVC(%)	TLC(%)	DLCO(%)	PaO2
Normal control	77.21±9.13	77.52±11.33	98.97±7.41	78.65±8.54	73.86±6.67
IIP	83.56±5.63*#	55.52±8.36*#	50.21±5.68*#	40.35±5.69*#	68.22±5.03*#
NSIP	80.24±4.32*	64.86±5.42*	69.45±3.26*	47.35±3.74*	70.64±5.45*

Table 4: Comparative analysis of lung function in the normal control group, NSIP group, and IIP group ($\bar{x}\pm s$).
*Note: *indicates P<0.05 compared with the normal control group, #indicates P<0.05 compared with the NSIP group.*

Spearman correlation analysis

Spearman correlation analysis showed that serum SDC4 and HRCT scores of patients in the IIP group and the NSIP group were significantly positively correlated (P<0.05). See Table 5.

HRCT scores	SDC4 (ng/ml)	
	r	*P*
IIP group	2.423	0.035
NSIP group	3.654	0.044

Table 5: Correlation between serum SDC4 level changes and chest HRCT fibrosis score ($\bar{x}\pm s$).

Analysis of the correlation between serum SDC4 and lung function

Serum SDC4 level was significantly positively correlated with FEV1 (P<0.05), and significantly negatively correlated with FVC, TLC, DLCO, and PaO2 (P<0.05). See Table 6.

Items	SDC4 (ng/ml)	
	r	*P*
FEV1 (%)	2.423	0.035
FVC(%)	-3.654	0.044
TLC(%)	-2.365	0.039
DLCO(%)	-3.687	0.023
PaO2	-3.897	0.048

Table 6: Analysis of the correlation between serum SDC4 and lung function.

Discussion

In patients with IIP, inflammation invades alveolar walls and adjacent alveolar cavities, resulting in thickening of the alveolar compartments and even pulmonary fibrosis. This leads to severe involvement of small airways, small blood vessels, alveolar epithelial cells, and capillary endothelial cells[5]. The pathogenesis of IIP is still unclear. The mainstream view believes that continuous alveolar epithelial damage, epithelial cell damage, and excessive repair and apoptosis are key factors in the formation of fibrosis[6]. Some scholars believe that IIP may be a kind of precancerous lesions. In the 2011 ATS/ERS diagnosis and treatment guidelines, lung diseases such as lung cancer, emphysema, and pulmonary embolism were proposed as the most likely complications of IIP[7]. The main pathological changes in IIP are myofibroblasts covering over-proliferating fibroblasts, proliferation of epithelial cells, and deposition of extracellular matrix proteins. Clinically, connective tissue diseases (rheumatoid arthritis, dermatomyositis, lupus erythematosus, etc.), collagen vascular diseases, and even some drugs can cause idiopathic interstitial pneumonia[8]. Therefore, in pathological diagnosis, it is particularly important that the clinical practices of alveolar lavage fluid examination, lung function examination, lung biopsy, and immunological examination of connective tissue diseases[9] are used to diagnose the type of pneumonia and improve the effects of treatment. Syndecan (SDCs) is a transmembrane proteoglycan, a member of the same family as Heparin sulfate (HSPG). The core protein of SDCs consists of the N-terminal extracellular region and the C-terminal intracellular and transmembrane regions[10, 11]. It can be used as a cell surface receptor to regulate adhesion-dependent signaling pathways and biological processes such as cell growth, proliferation, migration, adhesion, and extracellular matrix deposition. Syndecans (SDCs) are a family with 1-4 members.

SDC4 is a type I integral membrane protein with tissue-specific distribution encoded by 4 independent genes; it is covalently linked by the core protein and a long unbranched Glycosaminoglycan (GAG)[12]. Compared with other members of the family, SDC4 has higher structural and biological activity specificity and wider distribution. It is mainly found in multi-system tissue cells and is responsible for regulating various biological effects; it plays an important role in the signal transduction system and control of cell behavior on the cell surface.

The extracellular domain of SDC4 is where the GAG attaches[13]. Furini et al[14]. found that the expression of SDC4 can change in the event of inflammation, wounds healing, and various disease states. In inflammatory tissues, SDC4 is highly expressed in fibroblasts and endothelial cells, with levels significantly higher than the surrounding normal tissues. It will undergo protein lysis to shed the extracellular domain, and the released extracellular domain can be combined with fibroblast growth factor. The interaction of a series of growth factors[15] leads to cell growth and differentiation disorder, the proliferation of fibroblasts, and the formation of pulmonary fibrosis.

The results of this study showed that the SDC4 levels in the NSIP group and the IIP group were significantly higher than those of the normal control group, and the levels showed an increasing trend with the severity of the disease (P<0.05); the SDC4 level in the IIP group was significantly higher than that of the NSIP group, and the degree showed an increasing trend with the severity of the disease (P<0.05). Serum SDC4 and HRCT scores of patients in the IIP and NSIP groups were significantly

positively correlated with each other (P<0.05). Serum SDC4 level was significantly positively correlated with FEV1 (P<0.05), and significantly negatively correlated with FVC, TLC, DLCO, and PaO2 (P<0.05), showing that SDC4 plays an important role in the development of IIP.

In conclusion, SDC4 has a significant correlation with the severity of IIP. This information may lead to new ideas and vital advancements for the treatment of IIP. However, the samples in this study are limited, and the results are biased to a certain extent, so the results require further analysis and research.

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