



The significance of smoking as a risk factor for the disorder of the obstructive pulmonary pattern in the patients with systemic sclerosis

Značaj pušenja kao faktora rizika od poremećaja plućne funkcije kod bolesnika sa sistemskom sklerozom

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Abstract

Background/Aim. Systemic sclerosis (SSc) is a chronic systemic disease of the connective tissue. It is characterized by diffuse microangiopathy, increased activity and creating deposits of collagen in the skin and internal organs. Involvement of the lung function disturbances in SSc is a bad prognostic sign. The aim of our study was to investigate the association between smoking habits and lung function disorder in the SSc patients. **Methods.** The testing was conducted at the Clinic for Rheumatology and Immunology of the Military Medical Academy in 2016. In this study, we included 42 patients with the newly diagnosed SSc and the patients whose disease had been diagnosed earlier. **Results.** The patients were classified according to the smoking habits, 14 (33.3%) patients were nonsmokers, while 28 (66.7%) patients were current (23 patients) or ex-smokers (5 patients). We found no significant differences in examined parameters among smokers and nonsmokers. In addition, distribution of the patients with the obstructive pulmonary pattern revealed by spirometry was uniform between smokers and nonsmokers. The concentrations of C reactive protein (CRP) were significantly higher in the SSc patients with the obstructive pulmonary pattern. The patients with the obstructive pattern on spirometry had significantly lower values of forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC ratio, diffusing lung capacity for carbon monoxide (DLCO) and FVC/DLCO ratio. **Conclusion.** In our study, we concluded that in the SSc patients with the obstructive pulmonary pattern revealed by spirometry, there were no significant differences between smokers and nonsmokers. CRP is a significant predictor of the lung involvement existence in the SSc patients.

Key words:
scleroderma, systemic; lung diseases, obstructive; risk factors; smoking.

Apstrakt

Uvod/Cilj. Sistemska skleroza (SSc) je hronična sistemska bolest vezivnog tkiva. Karakteriše se difuznom mikroangiopatijom, povećanom aktivnošću i stvaranjem depozita kolagena u koži i unutrašnjim organima. Zahvatanje pluća u SSc je loš prognostički znak. Cilj rada je bio da se ispita povezanost navike pušenja i nalaza plućne funkcije kod bolesnika sa SSc. **Metode.** Ispitivanje je sprovedeno u Klinici za reumatologiju Vojnomedicinske akademije tokom 2016. godine. Bilo je uključeno 42 bolesnika oba pola sa novootkrivenom sistemskom sklerozom, kao i bolesnici kod kojih je bolest ranije dijagnostikovana. **Rezultati.** Bolesnici su bili podeljeni u grupe u pogledu navike pušenja: 14 (33,3%) bolesnika bili su pušači, a 28 (66,7%) bolesnika nepušači (23 bolesnika) ili bivši pušači (5 bolesnika). Nisu nađene značajne razlike ispitivanih parametara između pušača i nepušača. Distribucija bolesnika sa opstruktivnom nalazom na plućima, registrovanim spirometrijom, bila je jednoobrazna između pušača i nepušača. Koncentracije C reaktivnog proteina (CRP) su bili značajno više kod bolesnika sa SSc i opstruktivnim nalazom na plućima. Bolesnici sa opstruktivnim nalazom na plućima, registrovanim spirometrijom, imali su značajno niže vrednosti forsiranog vitalnog kapaciteta (FVC), forsiranog ekspirijumskog volumena tokom prve sekunde (FEV1), FEV1/FVC odnosa, difuzijskog kapaciteta za ugljen monoksid (DLCO) i FVC/DLCO odnosa. **Zaključak.** Kod bolesnika sa SSc i opstruktivnom nalazom na plućima, registrovanim spirometrijom, nema značajne razlike između pušača i nepušača. CRP je značajan prediktor za postojanje poremećaja plućne funkcije kod bolesnika sa SSc.

Ključne reči:
sklerodermija, sistemska; pluća, opstruktivne bolesti; faktori rizika; pušenje.

Introduction

Systemic sclerosis (SSc) is a chronic systemic disease of the connective tissue. It is characterized by diffuse microangiopathy, increased activity and creation of deposits of collagen in the skin and internal organs¹. Disease severity depends on the degree of damage to important visceral organs².

The affected respiratory system manifests events such as serositis, interstitial lung disease (ILD), pulmonary vascular disease, muscular weakness and infection³. Involvement of the lungs in SSc is a bad prognostic sign.

In systemic sclerosis, ILD can be seen in most patients⁴. As the first manifestation of the disease in SSc, ILD is very rare, and is associated with the presence of antibodies against topoisomerase I (anti-SCL-70 antibodies)^{5,6}.

In systemic sclerosis, involvement of the lungs is evident in the late stages of the disease^{4,7}.

A restrictive ventilatory defect is typical for patients with ILD. Static lung volumes are usually reduced in these patients⁸.

The determination of pulmonary function tests is important for diagnosis in the patients with ILD and SSc. These patients have decreased forced volume vital capacity (FVC) and diffusing lung capacity for carbon monoxide (DLCO).

After the perceived widespread bronchiectasis and peribronchial fibrosis during the autopsy in the patients with progressive SSc, it was concluded that there was a possible obstruction of the small airways in these patients⁸.

The aim of our study was to investigate whether there was an impact of smoking on the lung function disorder in the patients with SSc.

The hypothesis was that smoking was a leading cause that led to pulmonary function disorder involvement, but there were many factors that could cause the restrictive disturbances in the patients with SSc.

Methods

In our study, we tested the pulmonary function in two groups of patients – current or ex-smokers and non-smokers. The testing was conducted at the Clinic for Rheumatology and Immunology of the Military Medical Academy in 2016.

We included 42 patients with the newly diagnosed SSc and the patients whose disease had been diagnosed earlier. All patients met the American Rheumatism Association (ARA) criteria for diagnosis of SSc⁹.

The exclusion criteria were asthma, hypersensitivity pneumonitis and exposure to organic dusts.

Spirometry is performed using the spirometer Cardinal Health, Jaeger (Germany).

The pulmonary function testing included a measurement of FVC, forced expiratory volume in first second (FEV1), FEV1/FVC ratio, DLCO and FVC/DLCO ratio. The patients were classified according to the smoking habits: 14 (33.3%) patients were nonsmokers, while 28 (66.7%) patients were current (23 patients), or ex-smokers (5 patients). The patients were also compared on the basis of the presence or absence of an obstructive pattern on spirometry (obstructive: FEV1/FVC ratio < 80% + FEV1 < 80%, $n = 11$, nonobstructive: $n = 31$).

Statistical analysis

Normally distributed variables are presented as mean \pm standard deviation (SD) and categorical variables are presented as relative frequencies. Concentrations of C-reactive protein (CRP) were log-transformed prior to analyses in order to obtain a normal distribution. The data were compared by the Student's t test for continuous variables and by the χ^2 -test – contingency tables, for categorical variables. The correlations were assessed by the Pearson's correlation analysis. The logistic regression analysis was performed in order to explore the independent predictors for the development of obstructive pulmonary pattern in the patients with SSc. All statistical analyses were performed using the PASW Statistics version 18.0 and MedCalc Software version 11.4. The differences with $p < 0.05$ were considered to be statistically significant.

Results

Table 1 presents the general characteristics, concentrations of CRP as a marker of SSc and parameters of pulmonary function in the patients clustered by the smoking status. We found no significant differences in the analyzed parameters among the smokers and nonsmokers.

Table 1

General characteristics, C-reactive protein (CRP) and parameters of pulmonary function according to the smoking status in the systemic sclerosis patients

Patients	Smokers (n = 28)	Nonsmokers (n = 14)	<i>p</i>
Age (years)	51.57 \pm 11.06	51.43 \pm 10.13	0.968
Gender, male (%)	10.7	21.4	0.383
FVC (% predicted)	97.95 \pm 23.00	90.61 \pm 15.31	0.287
FEV1 (% predicted)	98.41 \pm 20.61	91.49 \pm 15.88	0.277
FEV1/FVC (% predicted)	96.91 \pm 13.80	94.69 \pm 11.84	0.610
DLCO (% predicted)	66.59 \pm 16.99	59.07 \pm 21.75	0.226
FVC/DLCO (% predicted)	73.45 \pm 16.49	66.14 \pm 25.30	0.265
Obstructive pattern on spirometry (%)	25.0	28.6	0.541
CRP (mg/L)*	2.30 (1.30–4.08)	2.80 (1.10–7.11)	0.709

Data are presented as mean \pm SD for continuous variables, or as relative frequencies for categorical variables and compared by the Student's t -test, or by the χ^2 -test, respectively. The values are presented as geometric mean (confidence interval) and log-transformed prior to analysis.

FVC – forced vital capacity; FEV1 – forced expiratory volume in first second; DLCO – diffusing lung capacity for carbon monoxide.

Table 2

General characteristics, C reactive protein (CRP) and parameters of pulmonary function according to the obstructive pattern on spirometry

Patients	Obstructive pattern (n = 11), mean ± SD	Nonobstructive pattern (n = 31), mean ± SD	<i>p</i>
Age (years)	57.27 ± 9.81	51.97 ± 11.03	0.665
Gender, male (%)	36.4	6.5	0.032
Smoking status (%)	63.6	67.7	0.804
FVC (% predicted)	83.12 ± 27.16	99.90 ± 16.50	0.020
FEV1 (% predicted)	82.99 ± 25.08	100.76 ± 14.54	0.007
FEV1/FVC (% predicted)	88.08 ± 14.26	99.04 ± 11.55	0.015
DLCO (% predicted)	52.91 ± 18.12	68.05 ± 17.64	0.020
FVC/DLCO (% predicted)	58.13 ± 23.99	75.58 ± 16.26	0.010
CRP (mg/L)*	4.79 (2.54–8.99)	1.95 (1.09–3.46)	0.031

For abbreviations see under Table 1.

Data are presented as mean ± SD for continuous variables, or as relative frequencies for categorical variables and compared by the Student's *t*-test or by the χ^2 -test respectively. The values are presented as geometric mean (confidence interval) and log-transformed prior to analysis.

In addition, the distribution of patients with the obstructive pulmonary pattern revealed by spirometry was uniform between the smokers and nonsmokers.

We analyzed the same parameters as previously in our patients in two groups (smokers or ex-smokers and non-smokers), divided according to the presence or absence of the obstructive pulmonary pattern revealed by spirometry. The obtained results are presented in Table 2.

In the group of smokers, there were 7 (25%) patients with the obstructive pattern on spirometry and 21 (75%) without it. In the group of non-smokers were 4 (29%) patients with the obstructive pattern on spirometry and 10 without it.

Expectedly, the patients with the obstructive pattern on spirometry (7 smokers or ex-smokers and 4 non-smokers) had significantly lower values of FVC, FEV1, FEV1/FVC ratio, DLCO and FVC/DLCO ratio. Both subgroups were uniform by age, but male sex was more prevalent among the carriers of the obstructive pattern.

Additionally, the concentrations of CRP were significantly higher in the SSc patients with the obstructive pulmonary pattern (smokers or ex-smokers and 4 non-smokers).

In order to achieve more in-depth insight into the associations of CRP levels with the parameters of pulmonary functions, we performed the correlation analysis. We found that concentrations of CRP were in the significant negative correlations with FVC, FEV1 and DLCO. Also, the CRP levels were in reciprocal relationships with FEV1/FVC and

FVC/DLCO ratios, although the statistical significance was not reached. The above-mentioned results are presented in Table 3.

Table 3

Correlations of concentrations of C reactive protein (CRP) with the parameters of pulmonary function in the systemic sclerosis patients

Parameters	Pearson's correlation coefficient	<i>p</i>
FVC (% predicted)	-0.358	0.030
FEV1 (% predicted)	-0.445	0.006
FEV1/FVC (% predicted)	0.183	0.278
DLCO (% predicted)	-0.413	0.011
FVC/DLCO (% predicted)	-0.313	0.059

For abbreviations see under Table 1.

Finally, we tried to find some independent predictors of obstructive pulmonary pattern development on spirometry. The multivariate logistic regression analysis was employed for this purpose. The results are presented in Table 4. Apart from the CRP concentration, the age and smoking status were also included in the model. The concentration of CRP was revealed as a significant predictor of development of lung function disorder involvement in the SSc patients. Neither smoking nor age of patients were recognized as the independent associates with the obstructive pattern assessed by spirometry.

Table 4

Multivariate logistic regression analysis of independent predictors of the obstructive pulmonary pattern in the sclerosis patients patients

Variables in model	OR	95 % CI	<i>p</i>
CRP	9.043	(1.006–81.282)	0.049
Age	0.944	(0.864–1.031)	0.198
Smoking habits (0 - no, 1 - yes)	1.548	(0.371–6.468)	0.549

CRP – C reactive protein; OR – odds ratio; CI – confidence interval.

Discussion

Lung involvement in SSc is inflammatory consequence of the underlying disease and characterized by the activation of alveolar macrophage, fibroblast proliferation and extracellular matrix, probably under the influence of uncontrolled cytokine. ILD is usually evaluated after the appearance of the respiratory symptoms³.

The degree of the lung parenchyma involvement in the patients with SSc can be estimated by the use of the pulmonary function tests.

The pulmonary function parameters that provide the best information are total lung capacity (TLC), FVC, FEV1, and DLCO³.

Monitoring of the FVC with the newly diagnosed SSc is useful, because its reduction indicates the occurrence of lung lesions and progression of the underlying disease¹⁰.

Greenvald et al.¹¹ proved that the non-smokers had greater decrease in TLC and static lung compliance compared to the current and ex-smokers.

Individual variability is important in disorder of the pulmonary function and it is not enough to know how smoking affects the pulmonary function.

Cherniack et al.¹² described that in the patients with idiopathic pulmonary fibrosis, which are non-smokers and former smokers, diffusing capacity per liter of lung volume (DLCO/VA) and FEV1/FVC ratio were significantly lower than in the patients who were smokers, while TLC and FVC were higher than in the non-smokers.

Our study shows that distribution of the patients with the obstructive pulmonary pattern, revealed by spirometry, is uniform between the smokers and nonsmokers, which can be explained in the way that the smoking habit in the patients with SSc is not the only reason for airway involvement. There are many factors that make the pulmonary function abnormal.

Steen et al.¹³ showed that in the patients with scleroderma, who smoked more frequently, severe obstructive

changes were revealed. Compared to the non-smokers, the patients who smoked and had restrictive lung disease had more severe disease. DLCO was significantly decreased in the patients-smokers compared with the nonsmokers.

A study showed that the pulmonary function in the patients nonsmokers with SSc was not different compared with the nonsmoking reference population¹⁴.

The patients with the obstructive pattern on spirometry had the significantly lower values of FVC, FEV1, FEV1/FVC ratio, DLCO and FVC/DLCO ratio. Both subgroups were uniform by age, but male sex was more prevalent among the carriers of the obstructive pattern. Also, in our study it was proven that the concentrations of CRP were significantly higher in the SSc patients with the obstructive pulmonary pattern.

Our study confirmed the findings of a large Canadian study⁵ reporting that the elevated baseline CRP levels were associated with the concomitant diffuse cutaneous involvement and severity of skin and lung involvement. In our study, the concentrations of CRP were the significant predictors of development of lung involvement in the SSc patients.

Conclusion

We concluded that in the SSc patients with the obstructive pulmonary pattern revealed by spirometry, there were no significant differences between smokers and non-smokers. CRP is a significant predictor of the lung involvement existence in the SSc patients, which can be explained in the way that the smoking habit in the patients with SSc is not the only reason for airway involvement. There are many factors that make the pulmonary function abnormal.

In the future, further research on the possible causes of the lung involvement in the patients with systemic sclerosis should be explored in some larger studies.

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