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ORIGINAL ARTICLE

BIOCHEMICAL PARAMETERS AS MONITORING MARKERS OF THE INFLAMMATORY REACTION BY PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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ABSTRACT

Background. Chronic obstructive pulmonary disease (COPD) is an airway inflammatory disease caused by inhalation of toxic particles, mainly cigarette smoking, and now is accepted as a disease associated with systemic characteristics.

Objective. The aim of this work was to investigate and compare selected biochemical parameters in patients with and without COPD.

Material and Methods. Observation group consisted of clinically stable patients with COPD (n = 60). The control group was healthy persons from the general population, without COPD, who were divided into two subgroups – smokers (n = 30) and non-smokers (n = 30). Laboratory parameters were investigated by automated clinical chemistry analyzer LISA 200th.

Results. Albumin in our measurements showed an average value of 39.55 g.l^{-1} in the patient population; 38.89 g.l^{-1} in smokers and in non-smokers group 44.65 g.l^{-1}. The average value of pre-albumin in the group of patients was 0.28 ± 0.28 g.l^{-1} and 0.30 ± 0.04 g.l^{-1} in smokers group. The average value of the orosomucoid in patients was about 1.11 ± 0.90 mg.ml^{-1}. In the group of smokers, the mean value of orosomucoid was 0.60 ± 0.13 mg.ml^{-1}. The level of C-reactive protein (CRP) in the patient group reached an average value of 15.31 ± 22.04 mg.l^{-1}, in the group of smokers was 5.18 ± 4.58 mg. l^{-1}. Prognostic inflammatory and nutritional index (PINI) in the group of patients showed a mean value of 4.65 ± 10.77 and 0.026 ± 0.025 in smokers.

Conclusions. The results of this work show, that the values of index PINI in COPD patients are significantly higher than in smokers (P <0.001). This along with other monitored parameters indicative inflammation as well as a catabolic process that occurs in the organism of patients with COPD.

Key words: *COPD, albumin, pre-albumin, C-reactive protein, orosomucoid, PINI index.*

STRESZCZENIE

Wprowadzenie. Przewlekła obturacyjna choroba płuc (POChP) jest chorobą zapalną dróg oddechowych spowodowaną inhalacją toksycznych związków chemicznych, pochodzących głównie z palenia papierosów, która charakteryzowana jest jako choroba ogólnoustrojowa.

Cel. Celem niniejszej pracy było oznaczenie we krwi chorych na POChP wybranych parametrów biochemicznych stanu zapalnego oraz porównanie ich stężenia w grupie zdrowych ludzi bez POChP.

Materiał i metody. Grupa badana składała się z klinicznie stabilnych pacjentów z POChP (n = 60). Grupę kontrolną stanowili zdrowi pacjenci z populacji generalnej, bez POChP, którzy zostali podzieleni na dwie podgrupy – palaczy papierosów (n = 30) i niepalących (n = 30). Parametry biochemiczne oznaczano z wykorzystaniem automatycznego analizatora LISA 200.

Wyniki. Średnie stężenie albumin w grupie chorych wynosiło 39.55 g.l^{-1} ; w grupie zdrowych palących 38.89 g.l^{-1} a w grupie zdrowych niepalących 44.65 g.l^{-1}. Średnie stężenie pre-albuminy w poszczególnych grupach pacjentów i zdrowych palących wynosiło odpowiednio 0.28 ± 0.28 g.l^{-1} oraz 0.30 ± 0.04 g.l^{-1}. Stężenie orosomukoidu w grupie chorych wynosiło 1.11 ± 0.90 mg.ml^{-1}. W grupie palących zdrowych osób średnio 0.60 ± 0.13 mg.ml^{-1}. Stężenie białka C-reaktywnego (CRP) w grupie chorych na POChP wynosiło 15.31 ± 22.04 mg.l^{-1}, a w grupie palących 5.18 ± 4.58 mg. l^{-1}. Prognostyczny wskaźnik odżywienia i stanu zapalnego - PINI *(Prognostic Inflammatory and Nutritional Index)* w grupie pacjentów wynosił średnio 4.65 ± 10.77 a w grupie osób palących 0.026 ± 0.025.

Wnioski: Wyniki niniejszych badań wykazały, że wartości PINI u pacjentów z POChP były statystycznie wyższe (p <0,001) niż w grupie osób palących. Uzyskane wyniki wraz z innymi monitorowanymi parametrami świadczą o stanie zapalnym jak również o procesie katabolicznym, który występuje w organizmie pacjentów z POChP.

Słowa kluczowe: *POChP, albumina, pre-albumina, białko C-reaktywne, orosomukoid, wskaźnik PINI*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an airway inflammatory disease caused by inhalation of toxic particles, mainly cigarette smoking, and now is accepted as a disease associated with systemic characteristics [16]. COPD can no longer be considered a disease only of the lungs [6]. It is associated with a wide variety of consequences, most notably systemic inflammation. Systemic inflammation is a risk factor for most of the complications that occur in these patients who suffer from cachexia, skeletal muscle abnormalities, hypertension, diabetes, coronary artery disease, cerebrovascular accidents. The origin of systemic inflammation in COPD is unresolved, although several potential mechanisms have been proposed [1].

Albumin is characterized as a negative acute-phase protein and its pool is affected by a number of inflammatory conditions and drugs [21]. Albumin is a serum hepatic protein with a half-life of 14-20 days [2, 4] and the main marker of visceral protein depletion. Supply of albumin in the body is 4-5 $g.kg^{-1}$. In the clinical context of albumin examination and its drop below 25-30 $g.l^{-1}$, it is among nutritional markers. In difficult conditions, the albumin acts as a negative marker and leads to a decline in the recent rise of CRP and other acute phase proteins [30]. Large losses of proteins, primarily albumin, occur in nephrotic syndrome, nephropathy, cirrhosis and chronic bronchitis [29].

Similar to albumin, pre-albumin is also a negative acute phase protein produced by the liver. The half-life of pre-albumin is much shorter (2-3 days) and its total body pool is considerably smaller than albumin [2, 23]. This very short half-life at the same time with high in tryptophan makes a pre-albumin very sensitive indicator of protein deficiency. The determination of pre-albumin to monitor the effectiveness of nutritional support is an appropriate parameter, especially in combination with albumin. Determination of pre-albumin is much more expensive than the determination of albumin, but it is an advantage in that it captures at least 44% of patients at risk of malnutrition even in the period when normal levels of albumin [29]. Pre-albumin is suitable especially for the evaluation of the catabolic state of chronically ill patients [14].

Orosomucoid is the classical acute phase protein exhibiting a 3-4 fold increase during inflammation, and the tissue damage. It is synthesized in the microvascular endothelium. Orosomucoid has a control and dampening effect on the inflammatory cascade, thereby protecting the tissues against damage in inflammation. In patients with proteinuria, orosomucoid predominantly excreted in the urine [19].

Serum level of CRP is increased in COPD patients. It is well known that this inflammatory marker causes a systemic inflammatory process and increases the chance of cardiovascular and cerebrovascular accidents, cachexia and osteoporosis. Therefore, it is recommended to measure the serum level of CRP in COPD patients during their routine clinical visits. These patients should be considered for a more aggressive treatment. Attenuation of systemic inflammation may offer new perspectives in the management of COPD and its comorbidities [12].

PINI index is calculated from four markers, two of which are inflammatory markers (C-reactive protein, and orosomucoid) and albumin, and pre-albumin are nutritional markers. Index PINI is a sensitive and universal means of diagnosing inflammatory diseases and malnutrition at a time subclinical stages of the disease. Healthy adults have PINI values below 1.0. In patients with inflammatory and malnutrition is PINI index progressively increasing [18].

The aim of this study was to investigate selected biochemical parameters in patients with COPD and compare their values with people without COPD. We focused on selected nutritional and inflammatory markers in COPD is typical for a systemic inflammatory response.

MATERIAL AND METHODS

The study was conducted on patients with chronic obstructive pulmonary disease (n = 60) from specialized St. Svorad Hospital Nitra Zobor, Slovakia, who were treated by means of hospitalization or outpatient basis. Observation group consisted of clinically stable patients acute deterioration of the patients was excluded from the reference file. The control group consisted of probands from the general population without COPD, acquired by random selection, who were divided into two subgroups: smokers (n = 30) and non-smokers (n = 30) represented individuals of both sexes. The research was approved by the ethics committee. We received the signed informed consent to be included in the study and carrying out appropriate investigations from all subjects.

The examination of the functional state of the lungs of COPD patients was performed using spirometry and Bodyplethysmographic to confirm the diagnosis and determine the stage of the disease**.** Patients were classified into different groups according to the severity of the disease (Gold I to IV). Lung function was evaluated using spirometer ©2005 ZAN® Meßgeräte, GmbH Germany.

Blood from probands was collected during hospitalization or outpatient examination. Laboratory parameters (albumin, pre-albumin, orosomucoid, C-reactive protein) were investigated by automated

clinical chemistry analyzer LISA 200th. Subsequently, the device calculated from these nutritional and inflammatory markers PINI-index. The device operates at wavelengths from 350-600 nm, in fully automatic mode with 3-stage quality control, automatic control of cuvettes cleanliness, with automatic sample dilution. The device includes software for quality control of the results. The analyzer is working after programming fully automatically.

The measured values were statistically processed and evaluated in a statistical program STATISTICA Cz. version 7.1. The most preferred test for statistical evaluation of our experiment which has a comparative nature is the *Kruskall-Wallis* test.

RESULTS AND DISCUSSION

Measurements of ventilatory capacity are fundamental to the assessment of respiratory health. Spirometric measurement is critical to the diagnosis and management of asthma, COPD, and restrictive lung disease. Respiratory disease is common, and the early effects of cigarette smoking, environmental pollution and occupational exposure demand clinical vigilance and objective measurement [20].

We performed spirometry (measuring of breath) in the group of patients to confirm the diagnosis (COPD), and to determine the disease stage. Table 1 shows average values of the main parameters of spirometry.

Table 1. The main spirometric parameters monitored in patients with COPD (n = 60)

	FEV_1 (l)	**FVC (l)**	**FEV_1/FVC (%)**
$\bar{x}$	1.15	2.14	52.57
± SD	0.63	0.61	16.95
Median	0.94	2.09	51.00
Maximum	3.20	4.11	94.00
Minimum	0.46	1.23	26.00
	% RH FEV_1	**% RH FVC**	**% RH FEV_1/FVC**
$\bar{x}$	40.03	57.93	70.50
± SD	20.63	15.02	22.84
Median	34.50	56.00	67.50
Maximum	99.00	106.00	125.00
Minimum	16	37.00	34.00

FEV_1 – forced expiratory volume in 1 second; FVC – forced volume vital capacity; FEV_1/FVC – ratio FEV_1 and FVC (Tiffeneau-Pinelli index); % RH – percentage of the reference values

If FEV_1 < 80%, it is considered a sign of significantly reduced lung function, in the studied group of patients, the mean FEV_1 was 1.15 ± 0.63 l (equivalent to 40.03 ± 20.63%), which signified that patients had significantly reduced lung function.

Measurement of FEV_1 is an important and accurate parameter because it is reproducible, as well as the objective indicator of lung function [23, 24]. In combination with measuring the ratio of FEV_1/FVC it differentiates the restriction and obstruction pulmonary diseases and provides accurate diagnosis of chronic obstructive pulmonary disease [25].

If the ratio of FEV_1/FVC is less than 70%, the diagnosis of COPD is confirmed [17].

FEV_1/FVC ratio (*Tiffeneau-Pinelli* index) reached in the studied group of patients with COPD the average value of 52.57 ± 16.95%, which clearly confirmed the diagnosis of COPD patients examined. On the basis of spirometry for confirmatory diagnosis, we also determined the stage of COPD by spirometry GOLD classification (I – IV stage). We found that patients with COPD were in the following percentage representation of disease: I. stage – 26.67%; II. stage – 71.67%; III. stage 0%, and IV. stage 1.66%. The similar observations came also *Singh* et al. [24].

Albumin, pre-albumin and CRP orosomucoid rank among the acute phase proteins. Inflammatory reactions in the body are accompanied by increased production of the proteins. For this reason, we consider monitoring the above parameters as important because with COPD patients the inflammation causes remodeling of the pulmonary parenchyma.

Nonspecific elevation of acute phase proteins in serum and other body fluids is caused by acute tissue injury. Initiating moments are the inflammation, rapidly growing tumors, as well as catabolic processes. Increasing levels of acute phase proteins explain the disintegration of body proteins. The subsequent increase in the supply of amino acids in the liver leads to the increased synthesis of acute phase proteins [5].

Albumin in our measurements showed an average value of 39.55 $g.l^{-1}$ in the patients group, 38.89 $g.l^{-1}$ in smokers group and in nonsmokers group 44.65 $g.l^{-1}$. Graphical representation of albumin levels ($g.l^{-1}$) in observed groups (P – patients; S – smokers; N – nonsmokers) is presented in Figure 1.

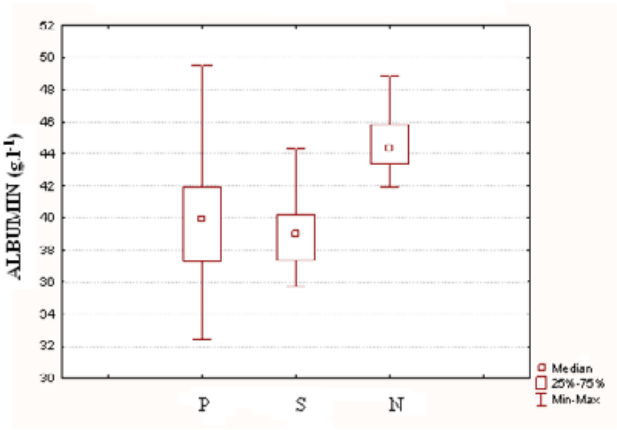

Figure 1. Albumin levels

We found statistically insignificant differences (P≥0.05) between groups of patients and smokers; significant differences (P<0.001) were found between the group of non-smokers and smokers and non-smokers and the group of patients. From the above it is evident that lower levels of albumin were found in groups of smokers and patients, which may reflect the present catabolic processes.

Similar findings also mentioned *Dzúrik* et al. [5] who argued that the concentration of albumin is decreased due to the catabolic degradation, while the permeability of capillaries is increased. Reduced values of albumin and transferrin represent the acute phase dysproteinemia.

The risk of malnutrition or diagnosed malnutrition found in most patients assessed may increase the likelihood of complications during treatment [28].

The pre-albumin level was determined in a group of patients and smokers. In the specified levels of pre-albumin were confirmed statistically highly significant differences (P<0.001) between the group of patients and smokers. The average value of pre-albumin in the group of patients was 0.28 ± 0.28 $g.l^{-1}$ and 0.30 ± 0.04 with smokers $g.l^{-1}$. Pre-albumin values in both groups were within normal ranges from 0.21 to 0.41 $g.l^{-1}$. Figure 2 presents graphs with similar levels of pre-albumin in the groups studied (P – patients; S – smokers).

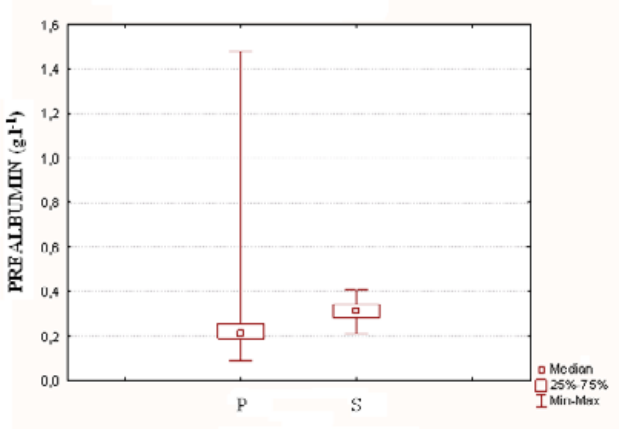

Figure 2. Pre-albumin levels

The level of orosomucoid (ORM) or α-1-acid glycoprotein is increased in inflammatory, cancer and infectious diseases [8]. This plasma protein is widely used as a downstream marker of inflammation and its synthesis is regulated by different proinflammatory cytokines [9, 15]. It is also widely recognized that COPD is an inflammatory disease [7, 11, 26, 27].

The average value of the orosomucoid in patients was about 1.11 ± 0.90 $mg.ml^{-1}$ (median 0.69 $mg.ml^{-1}$; maximum 3.37 $mg.ml^{-1}$, a minimum of 0.45 $mg.ml^{-1}$). In the group of smokers, the mean value of orosomucoid was 0.60 ± 0.13 $mg.ml^{-1}$ (median 0.58 $mg.ml^{-1}$; maximum 1.01 $mg.ml^{-1}$, minimum 0.40 $mg.ml^{-1}$) as it is shown in the Figure 3.

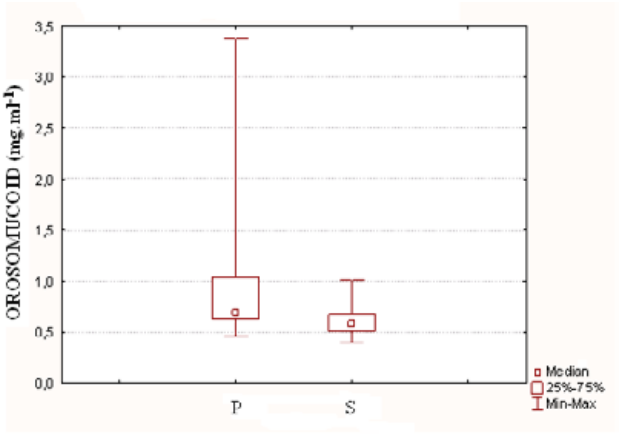

Figure 3. Levels of orosomucoid

By determination of orosomucoid in the blood of smokers and patients, we found higher levels of orosomucoid patients. The results were statistical significant (P <0.001).

The level of C-reactive protein (CRP) in the patient group reached an average value of 15.31 ± 22.04 $mg.l^{-1}$ (median 6.00 $mg.l^{-1}$; maximum 97.30 $mg.l^{-1}$; minimum 0.30 $mg.l^{-1}$), whereas in the group of smokers, the CRP mean value was 5.18 ± 4.58 $mg.l^{-1}$ (median 3.68 $mg.l^{-1}$; maximum 21.22 $mg.l^{-1}$; minimum 0.95 $mg.l^{-1}$). Normal levels of CRP range from 0 to 6.00 $mg.l^{-1}$. Between the groups of patients and smokers the significant difference (P <0.05) was found, as documented in Figure 4. Increases in CRP indicate the presence of inflammation. The amount of CRP level reflects the extent of inflammation, the severity and course of the disease.

We agree with the statement of *Burkhardtová* [3], who claims that in the improvement of health condition, the level of CRP is rapidly decreasing and confirms the success of therapy. It responds much faster than other markers indicating inflammation (e.g. sedimentation, leukocytes), therefore it is a relatively reliable indicator of inflammation.

Recent studies showed that a high level of C-reactive protein in individuals with COPD is associated with low health status in COPD patients [13].

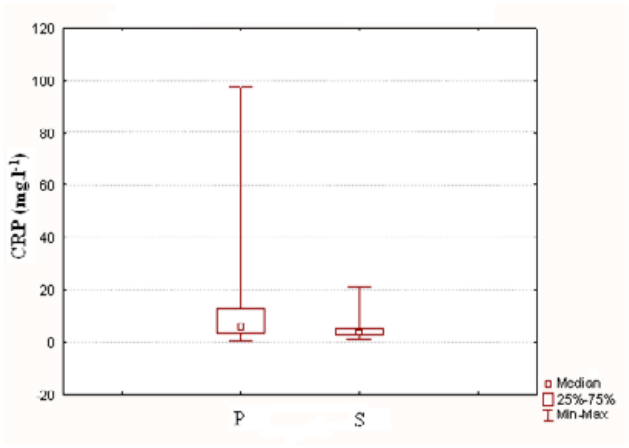

Figure 4. Levels of C-reactive protein (CRP)

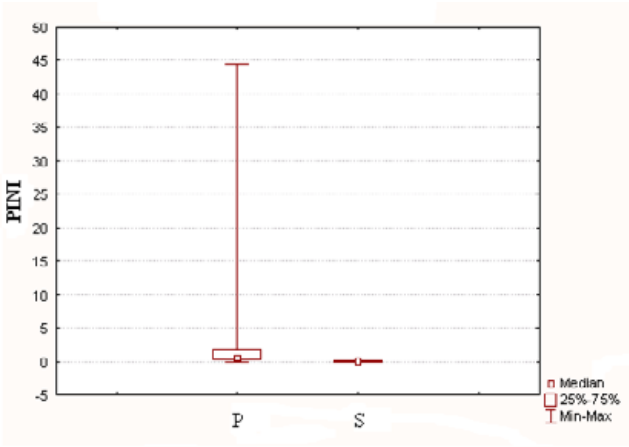

Figure 5. Levels of prognostic inflammatory and nutritional index (PINI)

Prognostic inflammatory and nutritional index - PINI is a sensitive and useful tool for the diagnosis of inflammatory diseases and malnutrition which is already in the subclinical stage of the disease, as proposed by the literary sources [10, 18].

PINI values were compared with values PINI in smokers where we found high statistical evidence values ($P < 0.001$).

PINI in the group of patients showed a mean value of 4.65 ± 10.77 (median 0.44; maximum 44.56; minimum 0.02). For smokers the mean value was of 0.026 ± 0.025 (median 0.016; maximum 0.103; minimum 0.003). From the comparison of PINI values between the two groups we found, that the PINI values with patients were significantly higher. It is an indication of the inflammation and the catabolic process. This process occurs in human patients as part of their disease - COPD. Moreover, we consider PINI as a suitable marker for monitoring the elderly at risk of severe complications that occur in the clinical stage of the disease and as a marker of mortality in seriously sick patients.

CONCLUSIONS

1. The results of this study show that the index values of prognostic inflammatory and nutritional index - PINI in COPD patients are significantly higher than in smokers, which was proved by statistically significant ($P<0.001$) differences between PINI values in observed groups. This observation was accompanied by other inflammation parameters and catabolic processes that occur in the organism of patients with COPD.
2. Each smoker is exposed to oxidative stress, with its negative effects on the cardiovascular and respiratory system. The progressive decline in lung function can only be averted by immediate cessation of smoking and the exclusion of other risk factors. The complex treatment comprising a pharmacological, rehabilitation treatment and nutritional intervention should be initiated.
3. Patients with COPD may be recommended a diet that contains enough energy, rich in amino acids, polyunsaturated fatty acids and antioxidant vitamins (C, E, *beta*-carotene), selenium and glutathione.

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Conflict of interest

The authors declare no conflict of interest.

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