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CLINICAL STUDY

Significance of plasma fibrinogen and malondialdehyde in the post-inflammatory period in patients with cystic fibrosis

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ABSTRACT

OBJECTIVES: Evaluation of selected inflammatory parameters and serum malondialdehyde (MDA) significance in the post-inflammatory period in adult patients with cystic fibrosis.

BACKGROUND: Laboratory biomarkers can be integrated into clinical practice as part of monitoring the effectiveness of treatment.

METHODS: After recovery from an acute exacerbation of lung infection, selected inflammatory parameters (fibrinogen, IL-1, IL-6, SAA, hs-CRP) and serum MDA were examined in 30 adult patients with cystic fibrosis. Their correlation with FEV1, frequency and duration of subsequent hospitalizations and 6-year prognosis in terms of mortality or need for lung transplantation was evaluated.

RESULTS: FEV1 negatively correlated with fibrinogen, but positively with MDA. No significant correlation with hs-CRP, IL-1, IL-6 and SAA was recorded. Plasma fibrinogen predicted the frequency and duration of subsequent hospitalizations. The 6-year prognosis was negatively associated with plasma fibrinogen whereas its association with MDA was positive. However, the prognosis of patients in the multivariate analysis was significantly associated only with FEV1.

CONCLUSION: Plasma fibrinogen examined in the post-inflammatory period is a marker of lung damage in patients with cystic fibrosis and can be used to predict the prognosis. The positive correlation of serum MDA with FEV1 in the post-inflammatory period may be important to the interpretation of treatment interventions *(Tab. 3, Fig. 2, Ref. 17)*. Text in PDF *www.elis.sk*

KEY WORDS: cystic fibrosis, acute inflammation, post-inflammatory period, oxidative stress, serum malondialdehyde, fibrinogen, prognosis.

Introduction

Cystic fibrosis is a congenital disease with a serious prognosis affecting the respiratory system (1). Repeated activations of the infectious inflammatory process in the lungs lead to a gradual deterioration of respiratory function (2). Exacerbation of the infection is associated with a significant increase in inflammatory parameters and oxidative stress (3). In contrast, successful treatment of acute infection leads to a reduction in the inflammatory response and increase in anti-inflammatory activity. The clinical significance of investigated parameters of inflammatory activity and oxidative stress may thus depend on the stage of the disease.

According to the results of our previous study, the administration of immunonutrition to adult patients with cystic fibrosis in the post-inflammatory period led to a significant decrease in serum amyloid A (SAA) but at the same time to a significant increase in plasma malondialdehyde (4). This result is difficult to interpret because in addition to the beneficial effect on inflammatory activity, the administration of immunonutrition was associated with an increase in oxidative stress.

The aim of this study was therefore to assess the significance of selected inflammatory parameters and plasma malondialdehyde in adult patients with cystic fibrosis in the post-inflammatory period. The relationships of selected inflammatory parameters and plasma MDA in the post-inflammatory period to FEV1, subsequent hospitalizations and the long-term prognosis were evaluated.

Patients and methods

The study involved 30 patients with the diagnosis of cystic fibrosis, who were at least 18 years old and signed the written informed consent. The study complies with the Helsinki protocol and was approved by the ethics committee of the University Hospital in Prague Motol. Patients were examined and followed-up in the

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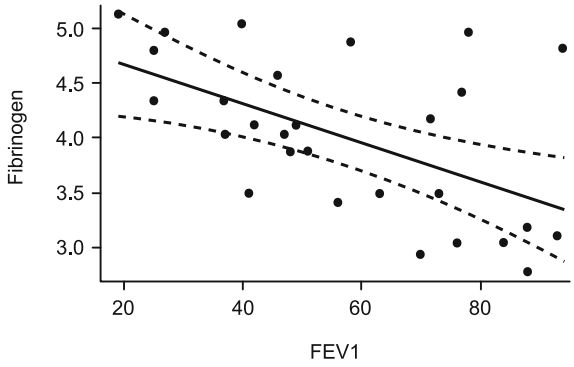

Fig. 1. The relation of plasma fibrinogen and FEV1 in the post-inflammatory period in the adult patients with cystic fibrosis. Pearson´s correlation coefficient, ρ = –0.5466; p = 0.0026. Fibrinogen in g/L. FEV1 percentage of normal value for age and gender.

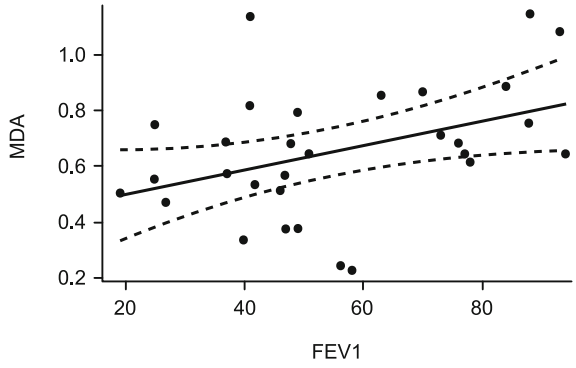

Fig. 2. The relation of serum malondialdehyde (MDA) and FEV1 in the post-inflammatory period in adult patients with cystic fibrosis. Pearson´s correlation coefficient 0.4039; p = 0.0269. MDA (malondialdehyde) in umol/L. FEV1 percentage of normal value for age and gender.

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All the patients were on long-term enteral nutritional support using Nutridrink (Nutricia, Denmark).

In the period after the exacerbation of the lung infection, clinical and laboratory examinations were performed, including spirometry, selected inflammatory parameters and serum malondialdehyde (MDA).

MDA was examined with the spectrophotometric method (Agilent Cary 60, Melbourne, Australia). SAA was examined using the immunonephelometric method (Immage 800, Canton, MA). IL-1 and IL-6 were examined with ELISA method (Affymetrix, eBioscience, San Diego, CA), and fibrinogen with ACL TOP750 (Werfen, USA)

Forced expiratory volume in 1 second (FEV1) was examined by spirometer MasterScope, (Jaeger, Germany). FEV1 was expressed as a percentage of normal value for age and gender.

For 6 years, the follow-up, frequency and duration of subsequent hospitalizations were recorded as well as the number of patients who passed away or were indicated for lung transplantation.

The significance of selected inflammatory parameters including fibrinogen and serum MDA examined in the post-inflammatory period was assessed in relation to FEV1, frequency and duration of subsequent hospitalizations, and mortality or lung transplantation.

Statistical evaluation

Numerical values are expressed as mean ± SD. The normality of the distribution of data was assessed by visual inspection of histogram and normal probability plot. Parametric continuous data were compared using Student t-tests and non-parametric data by using Mann–Whitney test. Pearson or Spearman bivariate correlation analysis was used for examining the relationship between parametric and non-parametric numeric variables, respectively. The effect of FEV1, BMI, plasma fibrinogen and MDA on study endpoints was investigated through logistic regression. P value of 0.05 was considered to be statistically significant. The analysis was performed in the statistical package R vision 3.6.3.

Results

Thirty patients were included in the study, 22 men and 8 women. The average age of the patients at the start of the study was 24 ± 3.6 years. Thirteen patients had diabetes mellitus, 14 were treated for metabolic bone disease, and pancreatic enzymes were prescribed to 27 patients.

At the initial examination, body weight of the patients was 57 ± 5.8 kg, BMI 18.8 ± 1.7 kg/m^2, CRP 13.7 ± 24.1 mg/l, SAA 26.1 ± 16.5 mg/L, IL-1 10.3 ± 6.6 mM, IL-6 8.4 ± 11.9 mM, plasma fibrinogen 4.01 ± 0.62 g/L, MDA 0.66 ± 0.24 uM, and FEV1 was 58 ± 17 % of the expected normal value.

FEV1 measured in the post-inflammatory period was negatively associated with plasma fibrinogen (Fig. 1) while being

Tab. 1. Correlation of clinical and laboratory parameters with duration of the subsequent hospitalizations.

	Age	BMI	hs-CRP	IL-1	IL-6	SAA	MDA	Fibrinogen	FEV1
CI	0.073	0.335	0.205	0.102	0.262	0.049	0.279	0.550	0.501
p	0.79	0.07	0.30	0.62	0.20	0.79	0.13	0.001	0.001

CI – correlation coefficient, BMI – body mass index, hs-CRP – high sensitivity CRP, IL-1 – interleukin 1, IL-6 – interleukin 6, SAA – serum amyloid A, MDA – malondialdehyde, FEV1 – forced expiratory volume in 1 second

Tab. 2. Correlation of clinical and laboratory parameters with the number of subsequent hospitalizations.

	Age	BMI	CRP	IL-1	IL-6	SAA	MDA	Fibrinogen	FEV1
CI	0.125	0.338	0.206	0.027	0.305	0.056	0.279	0.570	0.559
p	0.52	0.07	0.293	0.85	0.13	0.66	0.13	0.001	0.001

CI – correlation coefficient, BMI – body mass index, hs-CRP – high sensitivity CRP, IL-1 – interleukin 1, IL-6 – interleukin 6, SAA – serum amyloid A, MDA – malondialdehyde, FEV1 – forced expiratory volume in 1 second

Tab. 3. Unilateral analysis of the examined parameters with the long-term prognosis.

	Group 1 (n=19)	Group 2 (p=11)	p
Age (years)	24.6±4.8	24.8±4.8	0.89
Gender (No of women/ %)	2 (25%)	9(41%)	0.67
BMI (kg/m^2)	19.3±1.9	17.7±1.6	0.03
hs-CRP (mg/L)	7.6±8.7	25.0±36.0	0.19
IL-1 (mM)	11.0±7.5	8.5±3.9	0.39
IL-6 (mM)	6.2±8.9	12.4±15.4	0.74
SAA (mg/L)	24.7±15.0	27.0±18.5	0.74
Fibrinogen (g/L)	3.7±0.7	4.5±0.4	0.001
MDA (umol/L)	0.72±0.3	0.55±0.1	0.01
FEV1 (%)	65.6±18.3	38.5±15.9	0.001

positively associated with serum MDA (Fig. 2). However, FEV1 was not found to be correlated with hs-CRP, IL-1, IL-6 and SAA.

The follow-up lasted for 6 years. The endpoint was recorded in 11 patients (2 women and 9 men), particularly 7 patients died and 4 had lung transplant.

The correlations of CRP, IL-1, IL-6, SAA, MDA, plasma fibrinogen, BMI and FEV1 with the frequency and duration of the following hospital admission are shown in Tables 1 and 2.

The relations of endpoints (death or lung transplantation) to the examined parameters are shown in Table 3.

However, in the multivariate analysis, the presence of endpoints was significantly associated only with FEV1 (p = 0.001).

Discussion

Laboratory biomarkers can be integrated into clinical practice to improve the assessment of the severity of lung disease and to monitor the effectiveness of treatment in patients with cystic fibrosis (5–8). Some previous studies have shown that CRP, IL-1 IL-6, SAA and other blood pro-inflammatory parameters are associated with the severity of lung disease as assessed by spirometry (FEV1) in cystic fibrosis. Their changes also predicted the risk of subsequent exacerbations of lung infection (6–11).

However, the concentration of these parameters in the blood varies depending on the stage of the disease. The present study evaluated the association of selected inflammatory parameters and serum MDA in the post-inflammatory period with lung function (FEV1), frequency and duration of subsequent hospitalizations, as well as with the frequency of deaths or lung transplants in the period of 6 years. In contrast to acute infection exacerbation, the concentrations of hs-CRP, IL-6, IL-1, and SAA did not significantly correlate with FEV1 in the post-inflammatory period as well as with the long-term prognosis.

On the other hand, in addition to the negative correlation with FEV1, the levels of plasma fibrinogen were also significantly associated with the frequency and duration of subsequent hospitalizations as well as with the long-term prognosis. Although FEV1 is crucial in the assessment of the severity of respiratory function impairment and long-term prognosis, the concentrations of plasma fibrinogen may be a very useful parameter. In our cohort, the fibrinogen concentration below 4 g/l was associated with a good long-term prognosis. No patient with fibrinogen concentration below 4 g/l died or was indicated for lung transplantation in the next 6 years, and the number and duration of subsequent hospitalizations were less frequent than in patients with the latter parameter above 4 g/l. The role of fibrinogen in patients with cystic fibrosis is therefore more complex than just being a parameter of acute inflammation.

Plasma fibrinogen concentration is already considered to be a promising biomarker for chronic obstructive pulmonary disease (COPD). With the increase in severity of COPD, there is a graded increase in plasma fibrinogen concentration relative to controls. The plasma fibrinogen concentration is also associated with a more serious prognosis in patients with COPD (12). Surprisingly however, plasma fibrinogen has not been evaluated as a prognostic factor in patients with cystic fibrosis. The way fibrinogen affects the respiratory system in patients with cystic fibrosis may lie in hypersecretion of the bronchial mucosa in the respiratory system induced by activation of the EGF receptor signal cascade following fibrinogen binding to ICAM-1 (13).

Oxidative stress plays an important role in the pathogenesis of cystic fibrosis (14). According to previous reports, MDA levels examined in plasma as well as in sputum are elevated in patients with cystic fibrosis as compared to healthy controls (15). MDA levels are higher in patients with severe pulmonary dysfunction as compared to those with mild-to-moderate functional impairment (16).

Our previous study evaluated the impact of immunonutrition given after acute exacerbation of lung infection in the patients with cystic fibrosis. This nutrition intervention was associated with a decline in SAA and IL-6 but with an increase in serum MDA. It was also unexpected to find out that plasma MDA negatively correlated with IL-6, IL-1 and SAA (4). This was the reason to examine the significance of plasma MDA in the post-inflammatory period.

Surprisingly, the plasma MDA concentration examined in the post-inflammatory period positively correlated with FEV1. The explanation for this finding is not clear. Hypothetically, after the successful treatment of the acute exacerbation of pulmonary infection, the anti-inflammatory activity may predominate over pro-inflammatory processes, which might have led to a reduction in oxidative stress. The negative correlation of plasma MDA with the frequency of death or lung transplantation would be a consequence of its correlation to FEV1.

In another previous study, plasma MDA was increased when pancreatic enzymes were administered to malnourished patients with cystic fibrosis in the post-inflammatory period. This was related to an improvement in T cell function. However, no increase in plasma MDA was observed when pancreatic enzymes were administered prior to the exacerbation of the infection (17). Based on this information, it is likely that the clinical significance of plasma MDA level and its change as a result of treatment intervention is dependent on the time of examination. Therefore, an increase in plasma MDA collected in the post-inflammatory period due to medical intervention may not have a negative clinical impact, especially when the other significant parameters are positively affected.

The present study has limitations. In addition to the limited number of included patients, this is due to the fact that the moni-

tored parameters were not collected and assessed also outside the post-inflammatory period. Therefore, the significance of plasma fibrinogen and MDA in post-inflammatory period needs to be evaluated further.

Learning points

Plasma fibrinogen examined in the post-inflammatory period is associated with a deterioration in respiratory function and long-term prognosis in adult patients with cystic fibrosis.

The increase in plasma MDA in the post-inflammatory period induced by medical intervention may not have a negative impact on patients with cystic fibrosis.

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