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Matrix metalloproteinases-9 and tissue inhibitor of matrix metalloproteinases-1 in sarcoidosis patients

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Summary

Matrix metaloproteinases (MMPs) and their specific inhibitors - tissue inhibitors of matrix metalloproteinases (TIMPs) play an important role in pulmonary extracellular matrix destruction. Sarcoidosis is an inflammatory disease affecting multiple organs. It has been reported that MMP-9 and TIMP-1 levels were increased in bronchoalveolar lavage fluid and induced sputum of sarcoidosis patients. The aim of our study was to evaluate MMP-9, TIMP-1 and MMP-9/TIMP-1 complex concentrations and MMP-9/TIMP-1 ratio in sarcoidosis patients, their relationship with inflammatory markers and their ability do predict the existence of disease. We included 101 sarcoidosis patients and 50 healthy subjects. Serum samples were analyzed. Besides routine biochemical parameters, high-sensitive C-reactive protein (hsCRP), serum amyloid A (SAA), MMP-9, TIMP-1 and MMP-9/TIMP-1 complex concentrations were measured. MMP-9 ($P<0.05$), hsCRP, SAA and TIMP-1 ($P<0.001$) concentrations were significantly increased in patients whereas MMP-9/TIMP-1 complex was higher in patients, but with marginal significance. In sarcoidosis, TIMP-1 correlated significantly positively with inflammatory parameters ($P<0.05$). Uni-variate analysis showed that MMP-9, TIMP-1, hsCRP and SAA had the ability to predict the existence of sarcoidosis. In the model consisted of MMP-9, TIMP-1, hsCRP and SAA, only SAA remained significant predictor of disease ($P<0.01$). Results showed the significance of MMP-9 and TIMP-1 in sarcoidosis.

Keywords: sarcoidosis; matrix metalloproteinase-9, tissue inhibitor of matrix metalloproteinase-1, inflammation

Introduction

Normal lung functions are supported by extracellular matrix (ECM). Abnormal remodelling and destruction of ECM occurs in many pulmonary diseases. It has been described that matrix metaloproteinases (MMPs), a family of zinc and calcium dependent endopeptidases (1) and their specific inhibitors - tissue inhibitors of matrix metalloproteinases (TIMPs) play an important role in pulmonary ECM destruction (1, 2). TIMPs bind MMPs in a 1:1 manner to prevent their enzymatic activity (3). The expression of both MMPs and TIMPs is regulated by exogenous stimuli, cytokines, growth factors and cell-cell contact (2).

Sarcoidosis is an inflammatory disease affecting multiple organs primarily lungs with diverse clinical course. Extensive ECM remodelling reported in these patients occurs as a consequence of granuloma formation common to all disease manifestations (2). Henry et al (4) and Fireman et al (5) found that MMP-9 levels were increased in bronchoalveolar lavage (BAL) fluid and induced sputum of sarcoidosis patients. Shimada et al (6) demonstrated increased TIMP-1 concentration in BAL fluid that was associated with reduced pulmonary function in patients with sarcoidosis. In the study (5), TIMP-1 was increased in sputum of sarcoidosis patients, but with marginal significance. It is estimated that cellular source of MMP-9 and TIMP-1 may primarily be multinucleate giant cells localized in sarcoid granuloma, but also macrophages and epithelioid cells (7).

It has been considered that MMP-9/TIMP-1 complex represents the functionality of antiproteases system. Increased levels of MMP-9 bound to TIMP-1 are usually followed by increased TIMP-1 concentrations and indicate greater efficiency of TIMP-1 in neutralizing MMP-9 (8). MMP-9/TIMP-1 complex concentrations have been documented in patients with neutrophilic and eosionophilic asthma (8) and in chronic obstructive pulmonary disease (COPD) (9). Neutrophilic asthma having higher TIMP-1 concentration than eosinophilic asthma was also characterized by higher MMP-9/TIMP-1 complex (8). The study on the patients with COPD reported increased levels of MMP-9/TIMP-1 complex in exacerbation state of disease when compared with stable state or control subjects. However, to our knowledge, there are still no data describing MMP-9/TIMP-1 complex in sarcoidosis.

MMP-9/TIMP-1 ratio indicates a shift in the balance between the enzyme and its inhibitor in favour of MMP-9. It means that ratio would be increased in the state of increased proteases activity (4). Previous studies (4, 5) showed increased levels of this parameter in sarcoidosis patients when compared with controls although significant difference was not found in the study (4).

The aim of our study was to evaluate MMP-9, TIMP-1 and MMP-9/TIMP-1 complex concentrations and MMP-9/TIMP-1 ratio in sarcoidosis patients, their

relationship with inflammatory markers and their ability do predict the existence of disease.

Materials and methods

Subjects

In this study, we included 101 sarcoidosis patients from the Clinic for Pulmonary Diseases and Tuberculosis, Clinical Centre of Serbia, Belgrade. The diagnosis was established by clinical, radiological and histological findings (10). Patients underwent biopsy analysis that confirmed noncaseating epithelioid granulomatous inflammation in the appropriate organ/tissue. Other non-infectious and infectious causes of granulomas had been excluded. The exclusion criteria for the patients were the presence of cardiovascular disease, pulmonary (any other pulmonary disease except sarcoidosis), neurological, renal, hepatic, endocrine or malignant disease. Among patients, 84 were prescribed prednisolone, 14 were prescribed prednisolone together with methotrexate and 3 were received only methotrexate. Low daily dose of prednisolone was applied (median: 10 mg; interquartile range: 5-10 mg) whereas methotrexate was applied weekly (median: 5 mg; interquartile range: 5-10 mg).We also included 50 healthy subjects who were at their regular medical check-up at the local health center and accepted the participation in this study. The inclusion criteria for controls were the absence of any pulmonary, gastrointestinal, hepatic, renal, cardiovascular, malignant or endocrine disease.The study was planned according to the ethical guidelines stated in the Helsinki declaration. Written informed consent was obtained from all subjects prior to study entry. The research was approved by the institutional committee (Ethics Board) of Clinical Centre of Serbia.

Sample collection

After a 12-hour fasting period, venous blood samples were collected into serum sample tubes and then centrifuged (1500xg, 10 min at 4^0C) to obtain serum. Samples were aliquoted and stored at -80^0C. Aliquots were thawed immediately before analyses.

Biochemical parameters

Concentration of serum glucose, total protein, albumin, total calcium, urea, creatinine and uric acid as well as activity of alkaline phosphatase were assayed by routine laboratory methods (ILAB 300+analyzer, Instrumentation Laboratory, Milan, Italy). The latex-enhanced immunoturbidimetry method (Quantex hsCRP kit, BIOKIT, Barcelona, Spain) was used to measure the concentration of high-sensitive C-reactive protein (hsCRP) on an ILAB 600 analyzer. ACE was determined by commercially available colorimetric method (Fujirebio Diagnostics Inc.) with p-hydroxybenzoyl-glycyl-L-hystidyl-L-leucine as a substrate.The concentration of serum amyloid A (SAA) was determined by a commercially-available two-site enzyme linked

immunosorbent assay (ELISA) kit (Immunology Consultants Laboratory, Portland, OR, USA).

MMP-9, TIMP-1 and MMP-9/TIMP-1 complex concentrations were measured by commercially available enzyme-linked immunosorbent assay (ELISA) kits (Research and Diagnostics Systems, Minneapolis, MN, USA). The intra- and inter-assay coefficients of variation (CV) were as follows: 1.9% and 7.8% for MMP-9, 3.9% and 3.9% for TIMP-1, and 2.6% and 4.5% for MMP-9/TIMP-1 complex. MMP-9/TIMP-1 ratio was calculated.

Statistical analysis

To describe the data, we used means±standard deviation for normally-distributed data, geometric means and 95% confidence intervals for log-transformed normally-distributed data, median and interquartile range for non-normally distributed data and absolute frequencies for categorical variables. The normality of distribution of parameters was assessed using the Kolmogorov Smirnov test. Continuous variables having normal or log-normal distribution were compared using Student's t-test. The Mann Whitney test was used for comparisons of non-normally-distributed data. Differences between categorical variables were tested with Chi-square test for contingency tables. Spearman's correlation analysis was employed to determine possible correlations between examined parameters. The ability of parameters to predict disease was estimated using binary logistic regression analysis. All statistical analyses were performed using MS Excel, PASW Statistics Version 18.0 and MedCalc (version 11.4 Software, Belgium) software. The 0.05 probability level was considered significant in all statistical tests.

Results

Demographic and biochemical parameters of sarcoidosis patients and control group are given in Table 1. Patients and controls were matched according to age and gender. The concentrations of glucose, urea and creatinine were significantly lower whereas the concentrations of total proteins and albumin were significantly higher in patients group when compared to controls. HsCRP and SAA were significantly increased in patients and ACE activity was above borderline value of reference interval. (Table I)

Table I Basic biochemical characteristics and inflammatory parameters of sarcoidosis patients and control group

Parameter	Controls (N=50)	Sarcoidosis (N=101)	P[c]
Age (years)	47.3 ± 9.4	51.0 ± 10.9	0.057
Gender (m/f)	20/30	32/69	0.406[d]
Glucose (mmol/L)	[b]5.2 (4.8-5.5)	4.9 (4.5-5.6)	0.031
Urea (mmol/L)	6.21 ± 1.41	5.56 ± 1.56	0.015
Creatinine (μmol/L)	86.7 ± 12.0	81.5 ± 13.4	0.030
Uric acid (μmol/L)	344 ± 93	291 ± 86	<0.001
Total proteins (g/L)	69.1 ± 5.2	72.3 ± 5.1	<0.001
Albumin (g/L)	35.1 ± 1.5	43.2 ± 3.0	<0.001
Calcium (mmol/L)	/	2.35 ± 0.10	/
Alkaline phosphatase (U/L)	/	73.9 ± 23.5	/
hsCRP (mg/L)	[a]0.97 (0.75-1.24)	2.05 (1.63-2.56)	<0.001
ACE (U/L)	/	[b]53.0 (42.0-67.0)	/
SAA (μg/mL)	[a]2.64 (1.96-3.55)	9.94 (7.57-13.05)	<0.001

a – geometric mean and 95% confidence interval,

b – median and interquartile range

c – Student t-test, d – Chi square test

Results obtained for protease/antiprotease system are presented in Table 2. The concentrations of MMP-9 and TIMP-1 were significantly higher in sarcoidosis patients when compared with those obtained for controls. MMP-9/TIMP-1 complex was higher in patients, but with marginal significance. The ratio of MMP-9/TIMP-1 was lower in patients although without significant difference. (Table II)

Table II MMP-9, TIMP-1 and MMP-9/TIMP-1 complex concentrations and ratio MMP-9/TIMP-1 in sarcoidosis patients and controls

Parameter	Controls	Sarcoidosis	P[b]
MMP-9 (ng/mL)	[a]131.2 (109.5-152.0)	172.3 (152.3-195.3)	0.010
TIMP-1 (ng/mL)	143.0 ± 49.3	229.4 ± 104.3	<0.001
MMP-9/TIMP-1 complex (ng/mL)	[a]1.14 (0.74-1.75)	1.80 (1.39-2.34)	0.062
MMP-9/TIMP-1 ratio	[a]0.974 (0.817-1.160)	0.829 (0.733-0.938)	0.140

a – geometric mean and 95% confidence interval,

b – Student t-test

We performed Spearman's correlation analysis to test associations of MMP-9, TIMP-1, MMP-9/TIMP-1 complex and MMP-9/TIMP-1 ratio with ACE, hsCRP and SAA in sarcoidosis and controls. In sarcoidosis, TIMP-1 correlated significantly positively with all mentioned inflammatory parameters and MMP-9/TIMP-1 ratio was in inverse association with ACE. These results are given in Table 3. In control group, no significant associations were found between protease/antiprotease and inflammatory markers. (Table III)

Table III Association ofMMP-9, TIMP-1 and MMP-9/TIMP-1 complex concentrations and ratio MMP-9/TIMP-1 with inflammatory parameters in sarcoidosis patients

Parameter[a]	ACE (U/L)	hsCRP (mg/L)	SAA (μg/mL)
MMP-9 (ng/mL)	-0.001	0.118	0.046
TIMP-1 (ng/mL)	0.452**	0.216*	0.330*
MMP-9/TIMP-1 complex (ng/mL)	-0.034	0.066	0.088
MMP-9/TIMP-1 ratio	-0.248*	0.083	-0.099

a – Spearman correlation coefficient, *P<0.05; **P<0.01

In order to determine whether the measurement of protease/antiprotease and inflammatory parameters had the potential to predict disease, we used binary logistic regression analysis. In the uni-variate analysis, MMP-9, TIMP-1, hsCRP and SAA showed the ability to predict the existence of sarcoidosis. These results are presented in Table IV. However, when each of these parameters (MMP-9, TIMP-1, hsCRP and SAA) adjusted for the parameters presented in Table IV, only SAA remained significant predictor of disease (OR = 4.599; 95% CI = 1.150-18.392; P=0.031).

Table IV Binary logistic regression analysis of risk potentials for protease/antiprotease system and inflammatory markers

Parameter	OR	95% CI	P
MMP-9 (ng/mL)	1.003	1.000-1.007	0.041
TIMP-1 (ng/mL)	1.015	1.009-1.022	0.000
MMP-9/TIMP-1 complex (ng/mL)	1.060	0.971-1.158	0.195
MMP-9/TIMP-1 ratio	0.912	0.664-1.252	0.568
hsCRP (mg/L)	1.523	1.185-1.957	0.001
SAA (μg/mL)	1.252	1.066-1.469	0.006

The dependent variable was disease status sarcoidosis (1) comparing to control (0)

Discussion

In our current study, we found that concentrations of hsCRP, SAA (Table I), MMP-9 and TIMP-1 (Table II) were significantly higher in sarcoidosis when compared with controls. TIMP-1 correlated significantly with all mentioned inflammatory markers (Table III). HsCRP, SAA, MMP-9 and TIMP-1 showed the potential to predict sarcoidosis (Table IV), but only SAA in multivariate analysis remained significant predictor of disease.

As sarcoidosis is an inflammatory disease, it has been expected to observe increased values of hsCRP, ACE (11, 12) and SAA compared to controls (13, 14) and our results were in agreement with these findings (Table I). Increased concentrations of SAA may be a consequence of either increased production of proinflammatory cytokines that stimulate hepatic production of SAA (11) or activated cells in granulomas that also produce SAA (15).

Our result of significantly increased concentration of MMP-9 in sarcoidosis comparing to controls (Table II) may be due to the inflammatory processes that are associated with protease/antiprotease imbalance (2). It has been documented that multinucleate giant cells and macrophages found in granulomas (2, 4, 7) and epithelial cells (2) are the sources of MMP-9 which may initiate ECM breakdown and

remodeling. Henry et al (4) and Fireman et al (5) found that MMP-9 levels were increased in BAL fluid and induced sputum of sarcoidosis patients. MMP expression may be upregulated by increased production of proinflammatory cytokines (2). Additionally, it has been reported that SAA may induce MMP production in synovial fibroblasts of patients with rheumathoid arthritis (16, 17) and our finding of increased MMP-9 could be also supported by increase in SAA concentration.

We found significantly higher levels of TIMP-1 in sarcoidosis than in controls (Table II) and TIMP-1 showed significant positive associations with inflammatory parameters (Table III). In the study of Fireman et al (5), it was shown that TIMP-1 was higher in sarcoidosis than in controls, but with marginal significance. Nevertheless, Shimada et al (6) observed significantly increased concentrations of TIMP-1 in sarcoidosis patients with stage 2 when compared with patients in stage 1. This suggests that more pronounced inflammation occuring in stage 2 may contribute to higher levels of TIMP-1. Similar result of highest TIMP-1 concentration in sarcoidosis patients with stage 3 when compared with those in stage 1 and 2 (4) may additionally confirm the influence of inflammation on ECM proteins. The sources of TIMP-1 have been considered to be lymphocytes (18) and macrophages (19). Previous report (6) revealed that MMP-9 concentration and MMP-9/TIMP-1 ratio were not altered significantly by the stage of disease indicating that TIMP-1 may be more sensitive to inflammation than MMP-9. In this study, it was also shown that only TIMP-1 correlated significantly with vital capacity of the lung. Capacity of the lung can be infuenced by inflammation (6) and this could be an explanation for significant correlations obtained only between TIMP-1 and inflammatory parameters in our study. However, Piotrowski et al (20) found no significant correlations between neither MMP-9 nor TIMP-1 with lung function parameters.

According to our knowledge, the current study was the first to demonstrate the concentrations of MMP-9/TIMP-1 complex in sarcoidosis which was higher than in controls, but with marginal significance (Table II). On the other hand, MMP-9/TIMP-1 ratio was lower in patients than in controls with no significance (Table II).The complex is considered to represent functionality of antiproteases (8) whereas the ratio shows the balance between protease and antiprotease in favour of protease activity (4). Increased levels of MMP-9 bound to TIMP-1 are usually followed by increased TIMP-1 concentrations and indicate greater efficiency of TIMP-1 in neutralizing MMP-9 (8). The same authors (8) demonstrated that neutrophilic asthma having higher TIMP-1 concentration than eosinophilic asthma was also characterized by higher MMP-9/TIMP-1 complex. Our patients also had higher TIMP-1 concentration than controls with higher MMP-9/TIMP-1 complex. Previous study (9) on COPD patients also described increased levels of MMP-9/TIMP-1 complex in exacerbation state of disease when compared with stable state or control subjects. Nevertheless, our result of unsignificant

difference of MMP-9/TIMP-1 ratio in sarcoidosis was in accordance with the result obtained in the study of Henry and coworkers (4) where MMP-9/TIMP-1 ratios in sarcoidosis patients having less severe stages of disease did not differ significantly from healthy subjects.

We found that MMP-9 and TIMP-1 as well as hsCRP and SAA in univariate binary logistic analysis were able to predict sarcoidosis (Table IV). In the model consisted of variables listed in Table IV, it was shown that only SAA was the marker which significantly predict disease. The result showed that although MMP-9 and TIMP-1 were important in disease prediction and progression, the significance of SAA as a marker of granulomatous inflammation (15) was higher than the significance of matrix metalloproteinases and their tissue inhibitors. It has been documented that SAA induce transcription of MMPs mRNA (16, 17, 21) suggesting the importance of this molecule in regulating protease/antiprotease system and this was probably the reason why only SAA in multivariate analysis showed significant potential in sarcoidosis prediction.

In conclusion, we found significantly increased levels of MMP-9 and TIMP-1 in sarcoidosis patients. TIMP-1 correlated significantly with inflammatory parameters. MMP-9 and TIMP-1 had the potential to predict sarcoidosis, but only SAA retained this ability in multivariate analysis.

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Matriks metaloproteinaze – 9 i tkivni inhibitori matriks metaloproteinaza – 1 kod pacijenata sa sarkoidozom

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Kratak sadržaj

Matriks metaloproteinaze (MMP) i tkivni inhibitori matriks metaloproteinaza (TIMP) imaju značajnu ulogu u destrukciji plućnog ekstracelularnog matriksa. Sarkoidoza je inflamatorno oboljenje koje zahvata različite organe. Utvrđeno je da su koncentracije MMP-9 i TIMP-1 povećane u bronhoalveolarnom lavatu i sputumu pacijenata sa sarkoidozom. Cilj naše studije je bio da se odrede koncentracije MMP-9, TIMP-1 i MMP-9/TIMP-1 kompleksa, MMP-9/TIMP-1 odnosa u sarkoidozi, njihova povezanost sa parametrima inflamacije, kao i njihov potencijal za predviđanje postojanja bolesti. Ispitivanjem su obuhvaćeni 101 pacijent sa sarkoidozom i 50 zdravih ispitanika. Analizirani su uzorci seruma. Pored rutinskih biohemijskih parametara, merene su koncentracije visoko-osetljivog C-reaktivnog proteina (hsCRP), serumskog amiloida A (SAA), MMP-9, TIMP-1 i MMP-9/TIMP-1 kompleksa. MMP-9 ($P<0,05$), hsCRP, SAA i TIMP-1 ($P<0,001$) su bili značajno veći kod pacijenata dok je koncentracija MMP-9/TIMP-1 kompleksa bila veća, ali sa graničnom značajnošću. U sarkoidozi, TIMP-1 je značajno pozitivno korelirao sa inflamatornim parametrima ($P<0,05$). Uni-varijantna analiza je pokazala da su MMP-9, TIMP-1, hsCRP i SAA imali značajan potencijal za predviđanje postojanja bolesti. U modelu koji je sadržao MMP-9, TIMP-1, hsCRP i SAA, samo SAA je ostao značajan u ovom predviđanju ($P<0,01$). Rezultati pokazuju značaj MMP-9 i TIMP-1 u sarkoidozi.

Ključne reči: sarkoidoza; matriks metaloproteinaza-9; tkivni inhibitor matriks metaloproteinaza-1; inflamacija