MATRIX METALLOPROTEINASES (MMP-2, 3, 7, 9) AND THEIR TISSUE INHIBITORS (TIMP-1, 2) IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Introduction:

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by B-cell hyperactivity, the formation of pathogenic autoantibodies, and highly varied clinical manifestations that involves multiple organs including kidney[1]. The involvement of angiogenesis and angiogenic factors of SLE has been suggested[2]. Extracellular matrix remodeling, endothelial cell migration and proliferation, capillary differentiation and anastomosis are the sequential steps required for angiogenesis. Extracellular matrix components such as matrix metalloproteinases (MMP) have been implicated in angiogenesis[3]. MMPs are members of the metzincin superfamily of zinc-based proteinases. MMPs mediate both degradation of extracellular matrix components and cell proliferation and facilitate leukocyte function cells. MMPs are also involved in inflammation and immune system dysfunctions[4]. MMPs are inhibited by specific proteins - the tissue inhibitors of metalloproteinases (TIMPs)[5]. The balance between MMPs and their specific inhibitors, TIMPs, might direct the long-term disease course. MMPs and their inhibitors may play a role in pathogenesis of SLE and other connective tissue diseases [6, 7]. In this study, we investigated the serum levels of MMP-2, MMP-3, MMP-7, MMP-9, TIMP-1, and TIMP-2 in patients with SLE and healthy controls.

Aim:

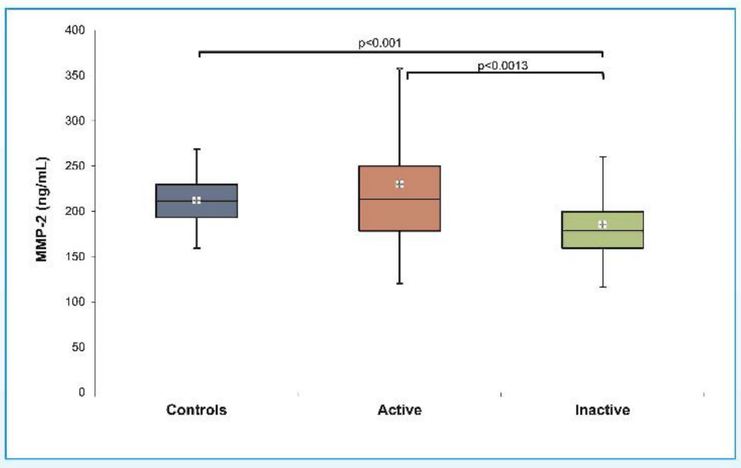
To assess whether serum levels of MMPs and TIMPs reflect MMP production and disease activity in SLE, we measured serum levels of MMP-2, MMP-3, MMP-7, MMP-9, TIMP-1, and TIMP-2 in active disease, in remission and compared these to healthy control subjects.

Methods:

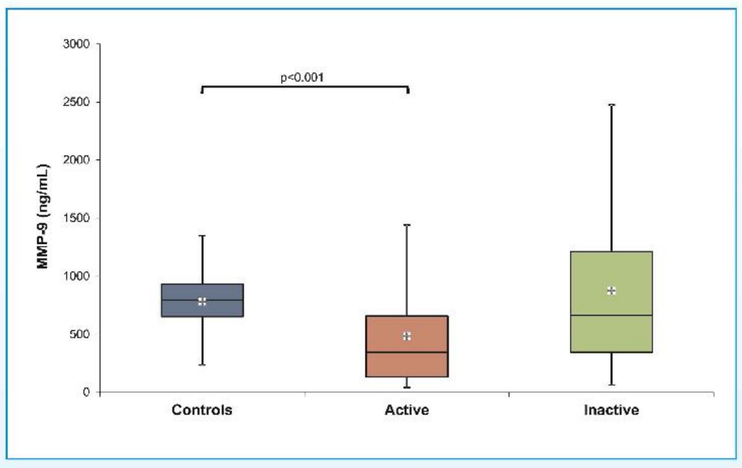
We studied 35 controls [34±11 years, 20 M, 15 F] and 97 patients with SLE: 47 patients with clinically active SLE and 52 clinically inactive disease and without infections [mean age 38 ± 13 years, 17 M, 80 F]. MMP-2, MMP-3, MMP-7, MMP-9, TIMP-1, TIMP-2 were assessed using enzyme linked immunosorbent assay (ELISA, R & D Systems). Results are expressed in nanograms per millilitre.
Routine biochemical parameters were measured using standard methods. Statistics: Statistical analyses were performed using
Statistics Toolbox™ MATLAB® software (The MathWorks™, Inc., Natick, Massachusetts, USA) - t-tests, ANOVA, Kruskal-Wallis ANOVA, univariate regression analysis. All results were considered statistically significant at $p < 0.05$.

Results:

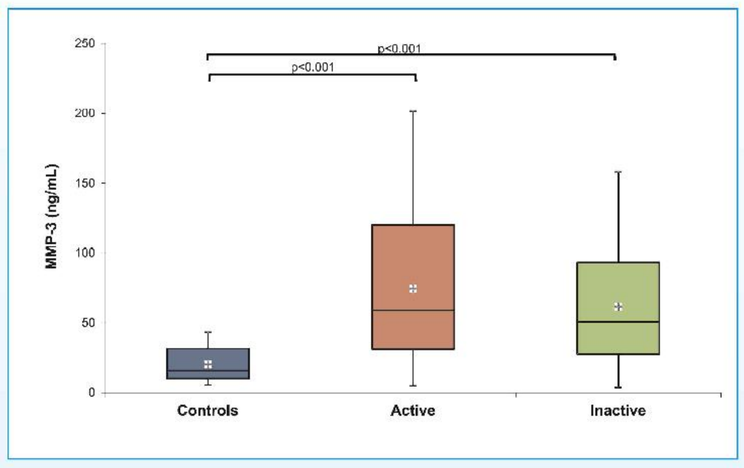
Levels of MMP-2 in SLE patients with active disease, with inactive disease, and controls.



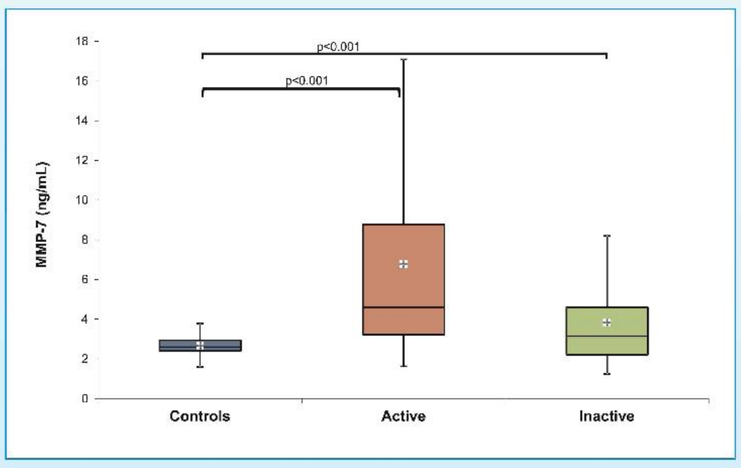
Levels of MMP-9 in SLE patients with active disease, with inactive disease, and controls.



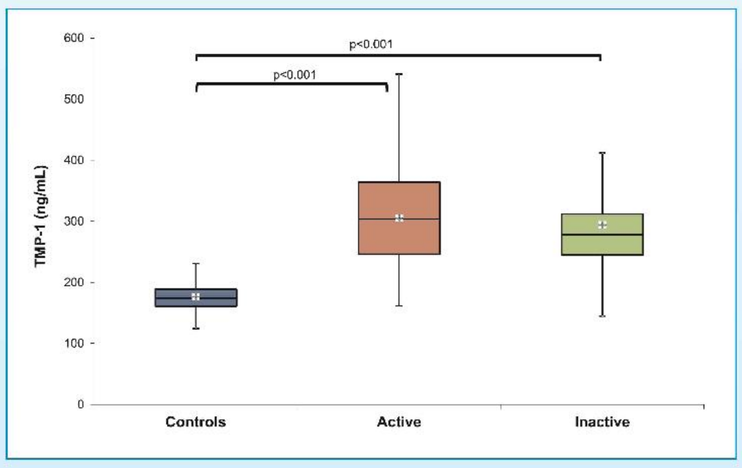
Levels of MMP-3 in SLE patients with active disease, with inactive disease, and controls.



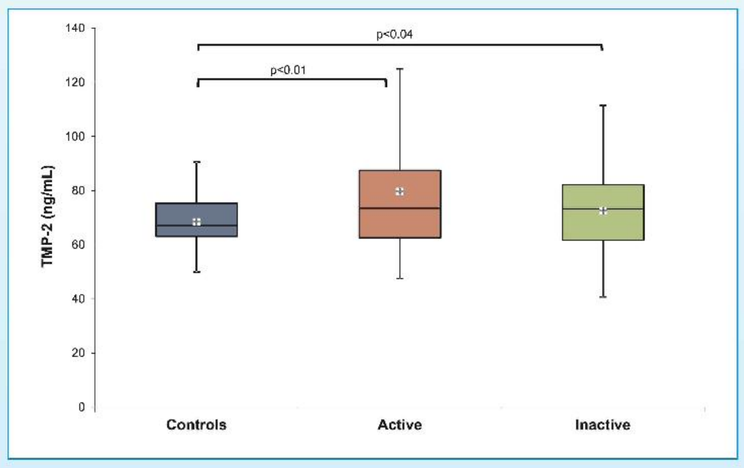
Levels of MMP-7 in SLE patients with active disease, with inactive disease, and controls.



Levels of TIMP-1 in SLE patients with active disease, with inactive disease, and controls.



Levels of TIMP-2 in SLE patients with active disease, with inactive disease, and controls.



Levels of MMPs and TIMPs in SLE patients with active disease, with inactive disease, and controls.

Parameter	Controls	Active	Inactive	p (t-test)
MMP-2 (ng/mL)	210 ± 27	232 ± 86	184 ± 36	0.001 (C vs I) 0.0013 (A vs I)
MMP-9 (ng/mL)	773 ± 302	477 ± 454	8 81 ± 650	0.001(A vs C)
MMP-3 (ng/mL)	20 ±11	75 ± 52	63 ± 38	0.001 (A, I vs C)
MMP-7(ng/mL)	2 ± 0.6	6 ± 5	4 ± 3	0.001 (A, I vs C)
TIMP-1 (ng/mL)	177 ± 26	302 ± 81	297 ± 84	0.001(A, I vs C)
TIMP-2 (ng/mL)	68 ± 10	79 ± 26	73 ± 13	0.04(I vs C) 0.01 (A vs C)

Compared with controls, the MMP-9 levels were lower in patients with active disease. The levels of MMP-3, TIMP-1 and TIMP-2 were increased in both in patients with active and inactive disease. Although, the levels MMP-7 were elevated in patients with inactive disease, the increase was even more pronounced in active patients.

Markers	Proteinuria	S-Creatinine [umol/L]	SLEDAI	CRP [mg/L]
MMP-2 [ng/mL]	r=0.4 p=0.001	n.s.	r=0.34 p= 0.01	r=0.2 p= 0.04
MMP-9 [ng/mL]	r=-0.21 p= 0.03	n.s.	r=-0.27 p= 0.01	n.s.
MMP-3 [ng/mL]	n.s.	r=0.27 p= 0.01	n.s.	n.s.
MMP-7 [ng/mL]	r=0.44 p= 0.001	r=0.63 p= 0.001	r=0.44 p= 0.001	n.s.
TIMP-1 [ng/mL]	n.s.	n.s.	n.s.	r=0.42 p= 0.001
TIMP-2 [ng/mL]	r=0.29 p= 0.003	n.s.	r=0.2 p= 0.03	r=0.23 p= 0.02

In SLE patients, the serum levels of MMP-2, MMP-7 and TIMP-2 correlated with proteinuria, while there was a negative correlation between proteinuria and MMP-9 (all $p<0.05$). MMP-3 and MMP-7 levels correlated with serum creatinine. A positive correlation was found between C reactive protein (CRP) and MMP-2, TIMP-1 and TIMP-2 (all $p<0.05$). Systemic Lupus Erythematosus Disease Activity (SLEDAI) correlated with MMP-2, MMP-7, and TIMP-2 and inversely with MMP-9.

Conclusions:

In this study, we evaluated circulating levels of MMP-2, MMP-3, MMP-7, MMP-9, TIMP-1, and TIMP-2 and in patients with active SLE, inactive SLE and healthy controls. This study suggests that circulatory levels of the studied MMPs and TIMPs fluctuate in SLE, and raised MMP-2, MMP-3, MMP-7, TIMP-1 and TIMP-2 probably reflect an increased inflammatory process, whereas lower concentrations of MMP-9 can result from accumulation of MMPs in the inflamed blood vessels and tissues. These findings point to putative relevance of serum MMPs and TIMPs in patients with SLE, specifically concerning kidney involvement present in this disease.

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Financial support:
The study was supported by research projects: PRVOUK -P25/LF1/2 and MH CZ-DRO VFN 64165.