Time courses of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases in systemic inflammation and revascularisation

Ph.D. thesis

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1. Introduction

Martrix metalloproteinases (MMPs) are structurally related, but genetically distinct zinc- and calcium-dependent endopeptidase enzymes. The history of MMPs started more than 50 years ago when Gros and Lapiere observed enzymatic activity during tadpole tail metamorphosis by placing a tadpole tail in a collagen matrix plate. The initially discovered enzyme was named interstitial collagenase (MMP-1) after its activity. Later MMP-1 was purified from human skin and was recognised to be synthesized as a zymogen. More than 25 members have been identified of these widespread enzyme family since 1962. The basic roles of MMPs are extracellular matrix degradation and remodelling. Besides these original functions, MMPs play an important role in tissue remodelling associated with various physiological and pathological processes such as morphogenesis, angiogenesis, tissue repair, cirrhosis, arthritis and metastasis. The first naturally occurring (endogen) inhibitor of matrix metalloproteinases was isolated from sera in 1970 and named as TIMP-1. Since 1970 four TIMPs have been described (TIMP-1, TIMP-2, TIMP-3, and TIMP-4). TIMPs are small and stable proteins with the ability to inhibit MMPs activity by forming non-covalent bond with MMPs in stoichiometric ratio (1:1). This type of inhibition is non-specific, therefore an inhibitor is able to act on many different enzymes. Besides regulating MMPs, TIMPs have several already proven functions for instance, in cellular differentiation and in apoptosis (anti-apoptotic effect).

The general importance of sepsis and systemic inflammatory response syndrome (SIRS) in medicine is not a question anymore. Sepsis related annual mortality in the developed countries has reached the level of cardiovascular diseases related mortalities. Due to clinical advances the mortality has decreased in tendency, but unfortunately the rising incidence of sepsis keeps the related annual mortality rate at the aforementioned high level. Sepsis associated health care expenditures are high as well. Therefore, researchers faced toward exploring pathophysiology of sepsis and SIRS to facilitate better therapies and outcomes. Ischemic-reperfusion injuries (IRI) are vastly related to surgical procedures. SIRS and sepsis might be the complications of IRI. However in the majority of cases, IRI associates to subclinical complications like postoperative cognitive dysfunction in carotid surgery. The importance of the MMP-TIMP system in SIRS, sepsis and in IRI is presumed, therefore we aimed to explore the time courses to facilitate better understanding and future therapies.

2. Aims

Aims of the investigation regarding burns related SIRS and its time course:

1. Identification of any significant changes of MMP-9 and TIMP-1 plasma concentrations.
2. Evaluation of plasma MMP-9-TIMP-1 activity dynamics (MMP-9/TIMP-1 ratio).
3. Exploring the predictive value of MMP-9, TIMP-1 and MMP-9/TIMP-1 ratio in sepsis development.

Aims of the investigation regarding severe sepsis and its treatment:

4. Identification of any significant changes of MMP-2, MMP-9, TIMP-1 and TIMP-2 plasma concentrations.
5. Exploring relationships between severe sepsis-related MMP-9 and TIMP-1 dynamics and SIRS related ones.
6. Evaluation of relationship between TIMP-1 plasma levels and mortality.
7. Description of MMP-TIMP activity changes during the course of treatment (MMP-2/TIMP-1; MMP-2/TIMP-2; MMP-9/TIMP-1; MMP-9/TIMP-2 ratios).
8. Identification of relationships between MMP-TIMP activity in severe sepsis and the course of the disease.
9. Exploring relationships between severe sepsis-related MMP-9/TIMP-1 ratio dynamics and SIRS related ones.

Aims of the investigation regarding the perioperative period of carotid endarterectomy:

10. Identification of any significant changes of MMP-9 and TIMP-1 plasma concentrations.
11. Evaluation of plasma MMP-9-TIMP-1 activity dynamics (MMP-9/TIMP-1 ratio).
12. Exploring the predictive value of MMP-9, TIMP-1 and MMP-9/TIMP-1 ratio in perioperative clinical complications.
13. Evaluation of the effects of pharmacological secunder prevention on MMP-9 and TIMP-1 plasma concentrations and on MMP-9-TIMP-1 system activity.

3. Methods

All the study protocols fulfilled the ethical guidelines of the Declaration of Helsinki (2003 and later 2008), and permission was obtained from the Institutional Scientific and Human Research Ethics Committee of the University of Pécs (4282.316-2216/KK15/2011, 2406/2005, 4330/2011, 4330/2013) prior to investigations.

3.1 MMP-TIMP system in burn-related SIRS, patients, inclusion and exlusion criteria

This retrospective study was performed using the remaining blood samples of burn patients (n=31) who participated in our previous studies. Only the blood samples of patients taken between March 2005 and May 2010 were investigated. The patients were treated uniformly, and they received no study medications. Inclusion and exclusion criteria were similar as in the original studies:

Inclusion criteria:

- burn injury affecting more than 15% of the body surface are (BSA)
- admission to our ward within 6 hours after injury
- patients met SIRS criteria.

Exclusion criteria:

- patients younger than 18 years old
- electrical injury
- bacterial infection on admission
- extreme burn severity (> 80%)
- previously documented chronic left heart or renal insufficiency
- known malignant disease
- documented previous medication affecting the inflammatory response of the body to burns (e.g. chronic use of corticosteroid).

3.2 MMP-TIMP system in severe sepsis, patients, inclusion and exclusion criteria

Patients (n = 38) treated for severe sepsis were included in our study. The diagnosis of severe sepsis was assessed by the New Simplified Acute Physiology Score (SAPS II), the Sequential Organ Failure Assessment (SOFA) score, and the Multiple Organ Dysfunction Score (MODS), also the American College of Chest Physicians/Society of Critical Care Medicine consensus was considered:

Inclusion criteria:

- 2 or more organ dysfunctions
- sepsis-induced hypotension and serum procalcitonin level > 5 ng/ml
- sepsis-induced tissue hypoperfusion

Exclusion criteria:

- patients younger than 18 years old
- known malignant disease
- documented previous medication affecting the inflammatory response of the body to sepsis (e.g., chronic use of corticosteroid)

3.3 MMP-TIMP system in the perioperative period of carotid endarterectomy (CEA), patients, inclusion and exclusion criteria

All patients scheduled for elective CEA at the Clinical Center of the University of Pécs, Hungary in 2012 were considered. They were included consecutively between January to December 2012. In 2012, a total of 66 patients were scheduled for elective CEA. Twelve patients were excluded as five met the exclusion criteria and seven refused to participate. Overall, 54 patients were included in the study.

Exclusion criteria:

- patients younger than 18 years old
- known malignant disease
- previous debilitating stroke

- psychiatric disorders
- documented previous medication affecting the inflammatory response of the body to sepsis (e.g., chronic use of corticosteroid)

3.4 Control groups

- In „MMP-TIMP in SIRS and severe sepsis" studies 10 and 17 healthy, age- and sex-matched individuals served as controls respectively.
- In „MMP-TIMP in CEA" study 20 atherosclerotic patients scheduled for outpatient ophthalmological examinations were invited as controls. No significant difference was observed regarding age, gender, medications, and coexisting diseases compared to the operated group, but controls were scanned with ultrasound to be free from significant carotid diseases. Controls were also free from symptoms and positive medical history regarding cerebral atherosclerosis and carotid diseases.

3.5 Blood sampling

Blood sampling was carried out once from every volunteer of the control groups. By SIRS, septic, and CEA patients blood samples were collected via radial artery cannula according to the following protocols:

- **SIRS patients:**

Blood samples were taken right after patients met SIRS criteria (day 1) and on the 5 consecutive days (days 2-6) at 7 AM before operations or painful dressing changes.

- **Severe septic patients:**

Blood samples were taken on admission (day 1) and on the 4 consecutive days (days 2-5) at 7 AM before painful interventions.

- **CEA patients:**

Samples were withdrawn at four time points (T1-4), T1: right after the insertion of the arterial line at the operating theater, T2: 60 min after the cross-clamp release, T3: first postoperative morning, T4: third postoperative morning.

3.6 MMP-TIMP assays

Plasma was isolated from heparin anticoagulated blood samples by low speed centrifugation at 4°C, and stored at −80°C until analyzed in a single batch. MMP-2, MMP-9, TIMP-1 and TIMP-2 were determined by the quantitative sandwich enzyme-linked immunosorbent assay (ELISA) techniques according to the manufacturer's instructions (R&D Systems, Inc, Minneapolis, MN). In comparison with standard MMP-2, MMP-9 and TIMP-1, TIMP-2 curves, the concentrations of MMP-2, MMP-9, TIMP-1 and TIMP-2 in plasma were determined spectrophotometrically (Multiskan Ascent microplate photometer, Type: 354; Thermo Electron Corporation, Waltham, MA) by reading the absorbance at 450 nm and were expressed as entire amounts in the plasma (nanograms per milliliter). The assays were executed at the Department of Surgical Research and Techniques, University of Pécs, Hungary.

3.7 Statistical analysis

The analyses were conducted by Statistical Package for the Social Sciences Statistics software, version 20. and 21. (SPSS, IBM Corporation, Armonk, NY, USA). Kolmogorov-Smirnov test was used to assess the distribution. In case of normal distribution, Student's t test was applied, otherwise, Wilcoxon signed-rank test or Mann-Whitney U test was used for the analysis of nonparametric data. Patients and controls were compared with Mann-Whitney U test, while intergroup analysis was conducted by Wilcoxon signed-rank test. Jonckheere-Terpstra test was used to detect significant trends. Correlations were analyzed with Spearman test. Data were expressed as minimum, maximum, median, and interquartile range (standard 25th-75th percentile). Using univariate and multivariate linear regression models, the influencing factors were evaluated on dependent variables. Values of $P<0.05$ were considered significant.

4. Results

4.1 Time course of the MMP-9-TIMP-1 system in burns related SIRS

By burns in general, the most frequent complications are sepsis and respiratory, cardiac, and renal failure. However, the leading causes of death during the trial period were cardiac (67%) and respiratory failure (33%), and we experienced no septic complications. Therefore, our study population could represent the postinjury SIRS period well. Six-day study interval has been chosen because we presumed that a 6-day period would open a wide time window that could be enough for detecting both the ascending and descending inflammatory responses. No correlations were detected between enzyme levels and common severity scores (Multiple Organ Dysfunction Score, Sequential Organ Failure Assessment, and Simplified Acute Physiology Score II) on admission.

Results of MMP-9 measurements

MMP-9 levels on admission and day 2 were significantly higher in burned patients than in healthy volunteers, whereas MMP-9 levels on days 4 to 6 were significantly lower in burned patients. MMP-9 showed a decreasing tendency during the whole study period ($P < 0.001$), its levels were significantly lower on days 2 to 6 compared to admission levels (Fig. 1a).

Results of TIMP-1 measurements

There was no significant difference between healthy controls and burned patients regarding TIMP-1 on admission, but it was significantly higher in burned patients on days 2 to 6. Comparing admission values with those of the following days TIMP-1 showed a significant elevation from the second day until the end of the study ($P < 0.001$) (Fig. 1b).

Results of MMP-9/TIMP-1 measurements

The time course of MMP-9/TIMP-1 followed the dynamics of MMP-9. MMP-9/TIMP-1 ratios were significantly higher in burned patients compared with healthy volunteers on admission and significantly lower on days 3 to 6. MMP-9/TIMP-1 ratio decreased continuously (P <0.001) (Fig. 1c).

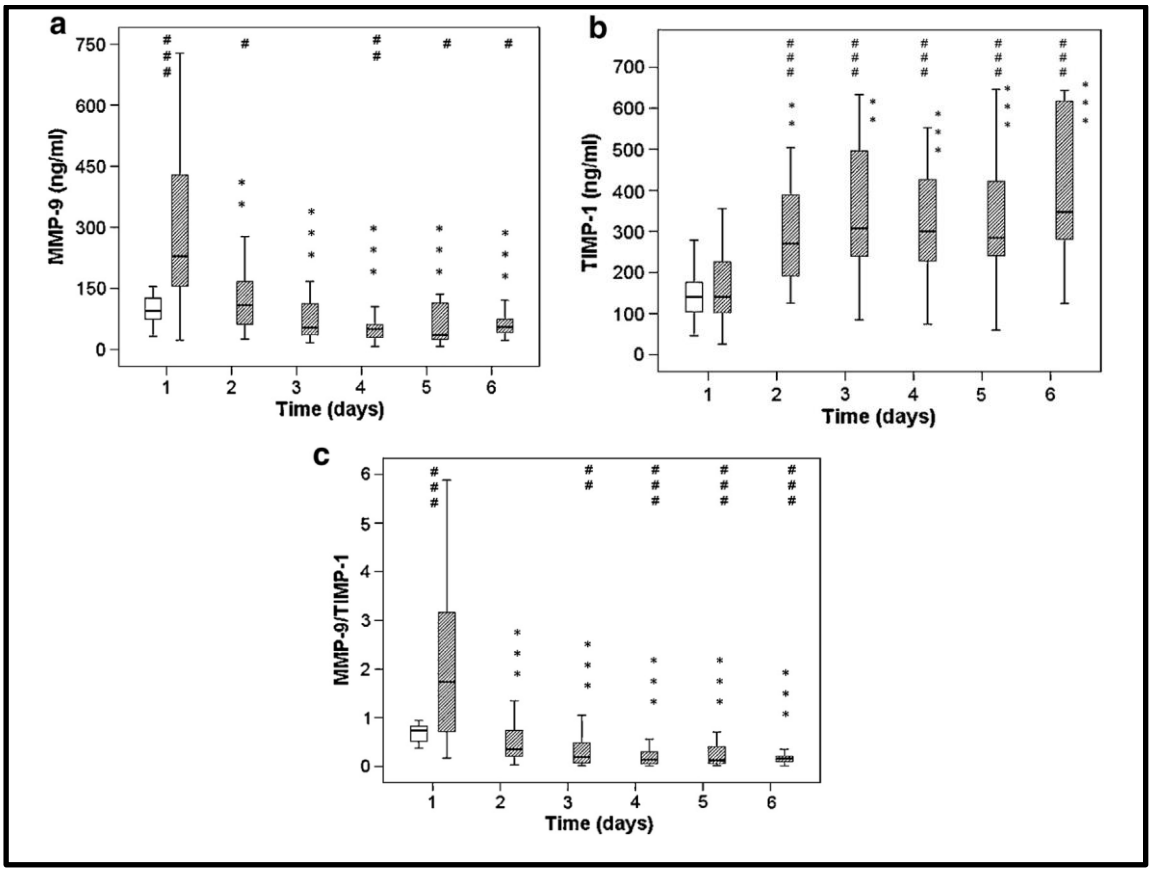

Fig. 1. MMP-9, TIMP-1 and MMP-9/TIMP-1 plasma levels in SIRS

Plasma levels of MMP-9 (a), TIMP-1 (b), and MMP-9/TIMP-1 ratio (c) in the control and in the patient groups. Data are expressed as minimum, maximum, median, and IQR (standard 25th-75th percentile and 5th and 95th confidence interval). Shaded boxes represent SIRS patients; white boxes show healthy control results. The "#" symbols show significant differences (P <0.05) in patients compared with controls (#P <0.05, ##P <0.01, ###P <0.001). Asterisks indicate statistical differences within the SIRS group compared with day 1 (⋆P <0.05, ⋆⋆P <0.01, ⋆⋆⋆P <0.001).

4.2 Time course of the MMP-TIMP system in severe sepsis

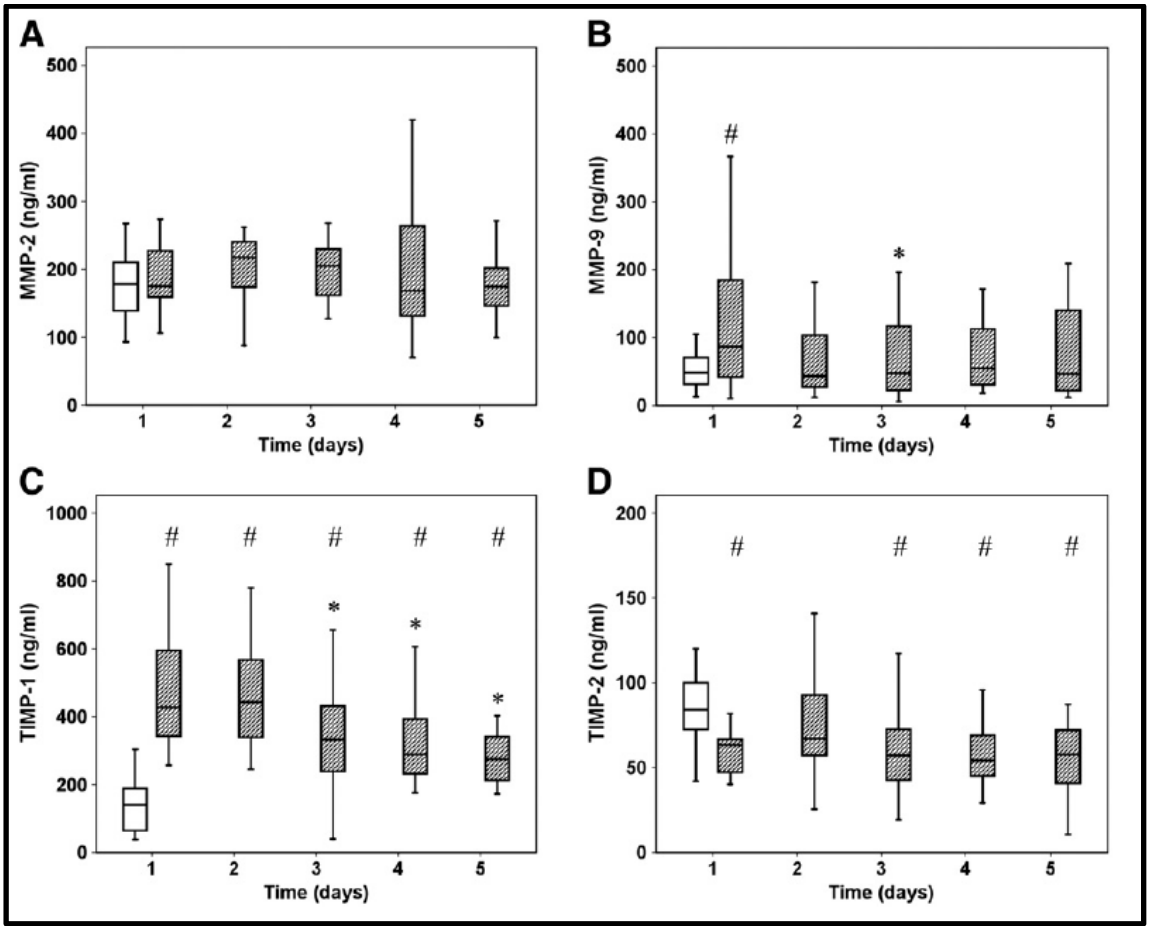

Fig. 2. MMP-2, MMP-9, TIMP-1 and TIMP-2 plasma levels in severe sepsis
Plasma levels of MMP-2 (A), MMP-9 (B), TIMP-1 (C), and TIMP-2 (D) on admission (day 1) and on the 4 consecutive days thereafter (days 2-5). Data are expressed as minimum, maximum, median, and interquartile range. Shaded boxes represent severe septic patients, white boxes show healthy control results. Asterisks indicate statistical differences ($P < 0.05$) inside the septic group compared to day 1. The "#" symbols show significant difference ($P < 0.05$) in severe septic patients compared to controls.

Results of MMP and TIMP measurements

MMP-2 levels were elevated although not significantly by days 2 and 3, but by day 4 they decreased to the control levels (Fig. 2A). The plasma MMP-9 levels were significantly higher ($P < 0.005$) on admission and reduced significantly by day 3 ($P < 0.009$). At the consecutive days, the MMP-9 remained at this nonsignificantly elevated level (Fig. 2B). The plasma level of TIMP-1 (Fig. 2C) was significantly elevated ($P < 0.002$-0.004) during the whole study period compared to controls. It decreased significantly from day 3 ($P < 0.006$). Except for day 2, the plasma level of TIMP-2 was significantly ($P < 0.05$-0.009) lower in septic patients (Fig. 2D).

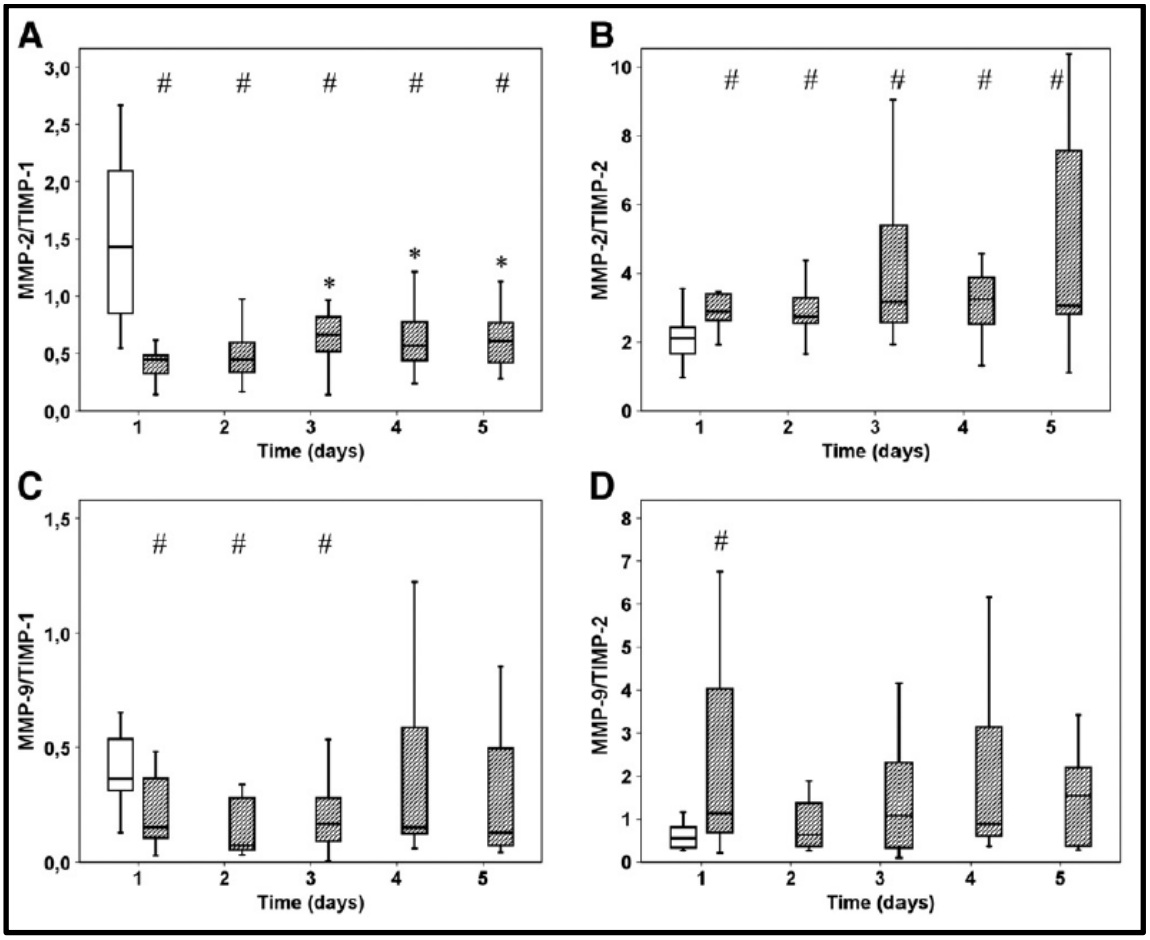

Fig. 3. MMP/TIMP plasma levels in severe sepsis

MMP-2/TIMP-1 (A), MMP-2/TIMP-2 (B), MMP-9/TIMP-1 (C) and MMP-9/TIMP-2 (D) ratios in plasma samples on admission (day 1) and on the 4 consecutive days thereafter (days 2–5). Data are expressed as minimum, maximum, median, and interquartile range. Shaded boxes represent severe septic patients, white boxes show healthy control results. Asterisks indicate statistical differences ($P < 0.05$) inside the septic group compared to day 1. The "#" symbols show significant difference ($P < 0.05$) in severe septic patients compared to controls.

Results of MMP/TIMP measurements

The MMP-2/TIMP-1 ratio (Fig. 3A) was significantly decreased during the whole observation period compared to controls ($P < 0.004$-0.002) and elevated significantly from day 3 ($P < 0.001$). MMP-2/TIMP-2 ratio was significantly elevated during all 5 days in septic patients ($P < 0.03$-0.006) (Fig. 3B). MMP-9/TIMP-1 ratio was significantly lower in septic patients compared to healthy controls on the first 3 days ($P < 0.05$-0.008) (Fig. 3C). MMP-9/TIMP-2 ratio was significantly ($P < 0.006$) elevated on admission in septic patients and remained above the normal values during the 5-day-long investigation (Fig. 3D).

4.3 Time course of the MMP-TIMP system in carotid endarterectomy

Laterality of the surgery, contralateral stenosis, gender, pre-existing diseases such as diabetes and hypertension, and nicotine abuse did not significantly influence plasma levels of MMP-9 or TIMP-1 in our study population. The potential effects of aspirin, adenosine diphosphate (ADP) receptor antagonists, and lipid lowering agents were evaluated on MMP-9 and TIMP-1 levels. Patients on ADP receptor antagonists (clopidogrel or ticlopidine) had lower ($P < 0.05$) circulating TIMP-1 levels at baseline (T1). Acetyl salicylic acid had no influence on the measured variables at any time point. Intraoperative bleeding and cross-clamp time (CCT) were selected for final linear multivariate analysis regarding MMP-9 levels at T3 and it was noted that 15 per cent of total variability could be explained by the model ($P < 0.05$). Patients requiring temporary shunt insertion had lower (Spearman rho=0.35, $P < 0.05$) TIMP-1 values at baseline (T1). Using stepwise logistic multivariate regression, diabetes, preoperative S100B and TIMP-1 levels were selected for a final model to predict shunting. Using a model including these variables, we were able to predict 100 per cent of shunting (Nagelkerke $R^2=1$; Hosmer and Lemeshow test $P = 1.00$).

Results of MMP, TIMP and MMP/TIMP measurements

The results regarding MMP-9, TIMP-1 and MMP- 9/TIMP-1 plasma levels are summarized in Fig. 4.

Except at T_1 the plasma level of TIMP-1 was significantly lower ($P < 0.05$) compared to controls during the whole study period. Comparing to the preoperative values (T_1), after reperfusion (T_2) we experienced decreased ($P < 0.05$) TIMP-1 levels and TIMP-1 remained at this significantly lower ($P < 0.05$) level at the first postoperative day (T_3), but returned almost to the baseline by T_4 (Fig. 4B). Plasma MMP-9 levels were increased ($P < 0.05$) compared to controls at T_1 and remained significantly elevated ($P < 0.05$) during the whole investigation. Significant elevation ($P < 0.05$) of MMP-9 levels was noted at T_3 compared to T_1 then values decreased to approximate T_1 levels by T_4 (Fig. 4A).

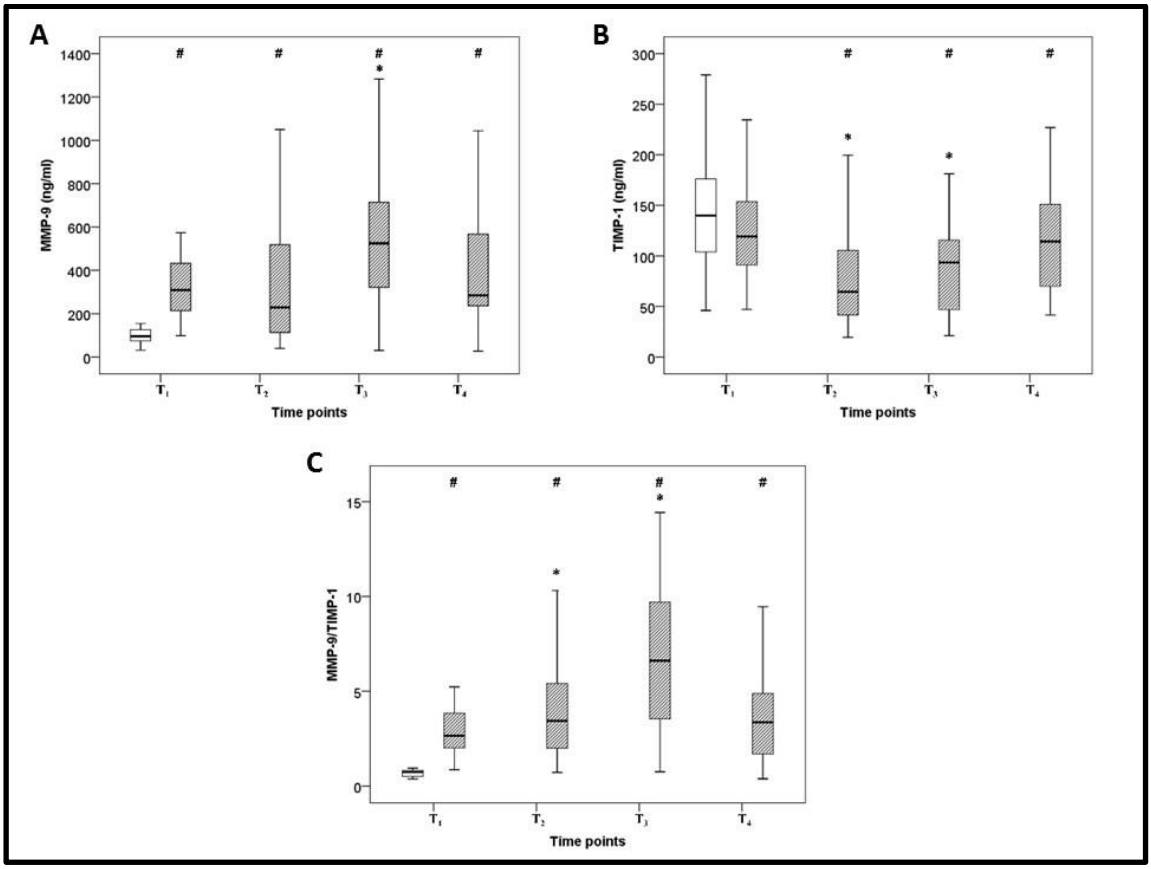

Fig. 4. MMP-9, TIMP-1 and MMP-9/TIMP-1 plasma levels in carotid endarterectomy (CEA)
Plasma levels of MMP-9 (A), TIMP-1 (B), and MMP-9/TIMP-1 ratio (C) in the control and in the patient groups. Data are expressed as minimum, maximum, median, and IQR (standard 25th-75th percentile and 5th and 95th confidence interval). Shaded boxes represent CEA patients, white boxes show control results. The "#" symbols show significant differences (P <0.05) in patients compared with controls. Asterisks indicate statistical differences (P <0.05) within the CEA group compared with T_1. T_1: preoperative values; T_2: 60 min after cross-clamp release; T_3: postoperative day 1; T_4: postoperative day 3.

MMP-9/TIMP-1 ratios were markedly increased (P <0.05) at all time points compared to controls. By reperfusion (T_2) the ratio of MMP-9/TIMP-1 elevated significantly (P <0.05) and by T_3 further elevation (P<0.05) was observed compared to T_1. By T_4 the MMP-9/TIMP-1 ratio decreased almost to the T_1 level (Fig. 4C).

Diabetes mellitus (DM) was associated with prolonged CCT (P <0.05). There was a positive correlation between CCT and age of the patients (Spearman rho=0.35, P <0.05). No significant correlation was observed between CCT and the measured variables (MMP-9, TIMP-1, MMP-9/TIMP-1, and S100B) at any time point. We selected diabetes, age of patients and nicotine abuse as independent variables for multivariate linear regression analysis, which showed that 19 per cent of total variability in CCT was explained by the selected variables (P <0.05).

5. Discussion

The MMP-TIMP system and the ECM are considered to be dynamic structures. Dynamic interactions of numerous different pathophysiological processes (release of inflammatory mediators, MMP activation, TIMP suppression/activation) are triggered by noxious stimulation (injury, infection, ischemia) of the human body. Pathological conditions (sepsis, POCD, stroke) or healing process will be initiated based on the results of the aforementioned complex interactions. These processes are linked in time as we managed to prove. The processes and markers of SIRS, severe sepsis and CEA should not be evaluated in subjectively selected time points, but time courses should be taken into consideration prior investigations to prevent questionable conclusions. Subjectively selected time points have been frequently used recently regarding MMP-TMP system in the literature, thus scientific information have gained might be questionable. Our investigations regarding the time courses of MMP-TIMP system have also used subjectively selected time points, but based on its frequency we gained valuable tendencies to help future investigations in the fields of SIRS, severe sepsis and CEA.

The predictive role of MMP's and TIMP's have raised recently in the literature regarding many different diseases and endpoints. MMP-9, TIMP-1, and MMP-9/TIMP-1 have been implicated regarding sepsis outcome, while in CEA related POCD MMP-9 suspected to be important. It is important to be highlighted that statistical significance between a biomarker and a disease/outcome should not be considered as strict causal relationship. The MMP-TIMP system has close and complicated interactions with many important systems (interleukins, cytokins), therefore interventions even with specific inhibitors could cause unanticipated, potentially disastrous results.

6. Novel findings

We have managed to prove the followings regarding MMP-TIMP system in SIRS and severe sepsis:

1. Dynamic changes could be observed in plasma MMP-9 and TIMP-1 concentrations, thus in plasma MMP-9-TIMP-1 activity by time course of SIRS and severe sepsis. We managed to describe the MMP-9-TIMP-1 patterns related to injury, SIRS, and sepsis. In concordance with the literature we believe, that the observed dynamics are related to the time courses of pro- and anti-inflammatory processes.
2. MMP-9 plasma levels increase right after injury, while TIMP-1 remains unchanged. The relationship between the extent of injury and MMP-9 might be suspected, but the evidences in the literature are still contradictory in this regard.
3. In SIRS the MMP-9 decrease and TIMP-1 increase in tendency, while in sepsis MMP-9 levels are normal/near normal and TIMP-1 levels are markedly increased. The MMP-9/TIMP-1 ratios have proven reduced in sepsis.
4. In remission of sepsis the TIMP-1 and the MMP-9/TIMP-1 normalize in tendency, while MMP-9 levels are still in normal range. Persistently elevated TIMP-1 and decreased MMP-9/TIMP-1 in this phase might be a marker of negative outcome according to the literature.
5. With the help of two different studies we managed to prove relationship between the time courses of MMP-9-TIMP-1 plasma kinetics in different, but related pathophysiological processes (injury, SIRS, sepsis), which result is in concordance with previous findings.
6. No changes could be observed in sepsis regarding MMP-2 plasma levels, thus its role in sepsis is unlikely.
7. Based on the aforementioned conclusion the role and usefulness of MMP-2 based activity markers (MMP-2/TIMP-1, MMP-2/TIMP-2) in sepsis are markedly questionable.
8. The plasma levels of TIMP-2 might be decreased in septic patients, however its importance is still unclear.

We have managed to prove the followings regarding MMP-TIMP system in CEA:

1. TIMP-1 levels proved to be normal prior surgery, while decrease thereafter, which might be the sign of increased ECM turnover after CEA.
2. MMP-9 levels are increased throughout the immediate perioperative period, which might be related to increased atherosclerotic plaque instability prior CEA, while to microembolization, hypoperfusion or reperfusion after CEA surgery.
3. Throughout the immediate perioperative period we managed to observe altered MMP-9-TIMP-1 activity (MMP-9/TIMP-1 ratios), which might be related to increased atherosclerotic plaque instability prior CEA, while to increased ECM turnover after CEA surgery based on the literature.
4. In the immediate perioperative period we managed to observe dynamic changes in MMP-9 and TIMP-1 plasma levels and in MMP-9/TIMP-1 ratios, which might be related to the time courses of related processes (pro- and anti-inflammatory cytokines, ECM turnover, BBB injury) due to microembolisation and/or IRI.
5. Significantly lower TIMP-1 plasma levels were observed prior CEA by patients taking ADP receptor blocker drugs regularly, however the reasons behind this finding are largely unclear.
6. Decreased TIMP-1 levels prior CEA might be predictive to intraoperative shunt requirement, which might be related to plaque instability through increased MMP-9/TIMP-1 activity. However, we could not find correlation between MMP-9/TIMP-1 ratios and shunt requirement, thus further studies are warranted for clarification.

7. Publications

Publications related to the Thesis

Original publications:

Mühl D[*], **Nagy B***, Woth G, Falusi B, Bogár L, Weber Gy, Lantos J: Dynamic changes of matrix metalloproteinases and their tissue inhibitors in severe sepsis. Journal of Critical Care. 2011; 26(6):550-555.

* = equal contribution, IF: 2.134, IF based on decision of first authors: **1.067**

Nagy B[*], Szélig L[*], Rendeki Sz, Loibl Cs, Rézmán B, Lantos J, Bogár L, Csontos Cs: Dynamic changes of matrix metalloproteinase 9 and tissue inhibitor of metalloproteinase 1 after burn injury. Journal of Critical Care. 2015; 30(1):162-166.

* = equal contribution, IF: 2.445, IF based on decision of first authors: **1.223**

Nagy B, Woth G, Mérei Á, Nagy L, Lantos J, Menyhei G, Bogár L, Mühl D: Perioperative time course of matrix metalloproteinase-9 (MMP-9), its tissue inhibitor TIMP-1 & S100B protein in carotid surgery. The Indian Journal of Medical Research. 2016;143(2):220-226.

IF (2015): **1.446**

Sum of original publications related impact factors: <u>3.736</u>

Abstracts:

Nagy B, Woth G, Mérei Á, Lantos J, Bogár L, Mühl D: Altered balance of matrix metalloproteinases and their natural inhibitors during severe sepsis. Infection. 2013;41S:7-8.

IF: **2.864**

Nagy B, Woth G, Mérei Á, Nagy L, Lantos J, Menyhei G, Bogár L, Mühl D: Mátrix metalloproteinázok és endogén inhibítoraik vizsgálata carotis endartherectomián átesett betegeken. Érbetegségek. 2013;20(4):96-97.

Nagy B, Woth G, Bogár L, Lantos J, Mühl D: Mátrix metalloproteinázok és szöveti inhibítoraik jelentősége szepszisben. Aneszteziológia és Intenzív Terápia. 2013;43(S1):12.

Nagy B, Woth G, Mérei Á, Nagy L, Lantos J, Menyhei G, Bogár L, Mühl D: When should we measure matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 regarding postoperative cognitive dysfunction after carotid surgery? European Surgical Research. 2014;52S:134.

IF: **2.474**

Nagy B, Woth G, Mérei Á, Nagy L, Lantos J, Menyhei G, Bogár L, Mühl D: A mátrix metalloproteináz-9 (MMP-9) – endogén szöveti inhibítor-1 (TIMP-1) rendszer perioperatív vizsgálata carotis endartherectomián átesett betegeken. Aneszteziológia és Intenzív Terápia. 2014;44(S1):4.

Sum of abstracts related impact factors: 5.338

Other publications

Original publications:

Woth G, **Nagy B**, Mérei Á, Ernyey B, Vincze R, Kaurics Z, Lantos J, Bogár L, Mühl D: The effect of Na-selenite treatment on the oxidative stress–antioxidants balance of multiple organ failure. Journal of Critical Care. 2014;29(5):883e7-e11.

IF: **1.995**

Mérei Á, **Nagy B**, Woth G, Zsidó N, Lantos J, Mühl D: Effects of therapeutic hypothermia and kinetics of serum protein S100B after cardiopulmonary resuscitation. Signa Vitae. 2015;10(2):7.

IF: **0.154**

Abstracts:

Woth G, **Nagy B**, Ernyey B, Kaurics Z, Vincze R, Bogár L, Mühl D: Szelén szupplementáció hatása a súlyos szepszis során kialakuló oxidatív stresszre. Aneszteziológia és Intenzív Terápia. 2013;43(S1):19.

Woth G, **Nagy B**, Mérei Á, Ernyey B, Kaurics Z, Vincze R, Lantos J, Bogár L, Mühl D: The effect of sodium selenite substitution on oxidative stress markers and antioxidants in severe sepsis. Infection. 2013;41S:57.

IF: **2.864**

Mérei Á, **Nagy B**, Woth G, Zsidó N, Lantos J, Mühl D: Terápiás hypothermia effektusa és protein S100B kinetika reanimációt követően. Aneszteziológia és Intenzív Terápia. 2014;44(S1):15.

Woth G, **Nagy B**, Rideg O: Többszervi elégtelen betegek plazma szabad DNS szintje fokozott Gram-negatív bakteriális fertőzésekben. Aneszteziológia és Intenzív Terápia. 2014;44(S1):14.

Nagy B, Woth G, Mérei Á, Lantos J, Bogár L, Mühl D: Dynamics of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) after cardiopulmonary resuscitation. Resuscitation. 2015;96S:137.

IF: **5.414**

Sum of impact factors in total: <u>19.501</u>