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## **Dynamic changes of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) after burn injury**

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## Introduction

Matrix metalloproteinase (MMP) and tissue inhibitor system (TIMP) has a key role in the wound healing process and in remodeling<sup>1-7</sup>. Wound extracellular matrix is a key regulator of cell adhesion, migration, proliferation, and differentiation during cutaneous repair. The amount and structure of normal wound extracellular matrix are determined by a dynamic balance among overall matrix synthesis, deposition, and degradation. MMPs are one family of structurally related enzymes that have the collective ability to degrade nearly all extracellular matrix components. The MMPs are broadly categorized into collagenases, gelatinases, stromelysins, and membrane-type MMPs by their substrate specificity<sup>5</sup>.

Severe burns generally associated with systemic inflammatory response syndrome (SIRS) with attributed alteration of pro- and anti-inflammatory cytokines in the early post insult period<sup>8-9</sup>. Cytokines and growth factors can influence the expression of MMPs and TIMPs significantly<sup>10</sup> and therefore the balance of MMP-TIMP system could be altered during the early post-injury period. MMPs are able to modulate the inflammatory response, they are responsible for migration and extravasation of leukocytes mainly due to degradation of basal membrane<sup>11</sup> but according to recent evidence they are also considered as signaling proteases. TIMPs can activate granulocytes and are able to protect inflammatory cells from apoptosis<sup>12</sup>.

MMPs and TIMPs have been evaluated extensively in sepsis<sup>13-16</sup> which is a feared and commonly fatal complication in burned patients. The prognostic importance of TIMP-1 has been proven and the time course has been recently described in severe septic patients<sup>15-16</sup>. It has been proven in an animal burn model that MMP-9 enzyme activity is significantly increased after thermal injury and the basal lamina damage is reversed by inhibition of MMP-9 by doxycycline<sup>17</sup>. MMP-9 disintegrates the endothelial basal lamina of the blood brain barrier so it can be responsible for increased permeability and it may play role in the formation of the observed cerebral oedema in peripheral thermal injury<sup>18</sup>.

In human studies the increase in MMP-9 levels was detected in the oedema fluid on day 4<sup>2</sup>. In a metaanalysis of three studies 1.4-fold increase of serum TIMP-1 levels was found after burn injury

<sup>19</sup>. Patients with extended hypertrophic scars after burn trauma presented a significantly higher TIMP-1 concentration in their sera than the other patients. There was no significant difference in the relative expression of mRNA of MMP-9 in scar tissue and keloids in comparison to non-scarred skin tissue <sup>6</sup>. In the study of Dasu and associates serum levels of MMPs and their tissue inhibitors were studied in burn patients over time. MMP-9 levels showed significant increase on day 21 <sup>20</sup>. TIMP-1 levels showed a significant increase from day 3 after burn injury <sup>6,20</sup>. In another study <sup>21</sup> serum levels of MMP-9 showed a significant elevation only between days 3 and 14 in patients with burn wounds. Serum TIMP-1 levels were elevated from day 1 to 6 months after injury. The elevated systemic TIMP-1 concentration was thought to be responsible for pathological scar formation <sup>21</sup>. Nowadays, this enzyme system is implicated as a new class of biomarkers with different expression pattern in many pathological conditions. No data are available in severe burned patients on the time course of MMP-TIMP system in the early post burn period. There have not been investigations into the difference between survivors and non-survivors. The aim of our study was to provide these important and missing data to facilitate better understanding of the underlying process in burn injury.

## **Materials and methods**

### *Subjects and study design:*

The study protocol was completed in accordance with the ethical guidelines of the 2003 Declaration of Helsinki. After receiving permission from the local ethics committee (4282.316-2216/KK15/2011), this descriptive study was performed using the remaining blood samples of patients who participated in our previous studies. Only the blood samples of patients taken between March 2005 and May 2010 were investigated. Ten healthy, age and gender matched individuals served as control. The patients were treated in uniform way and they received no study medications. Inclusion and exclusion criteria were similar as in the original studies. Inclusion criteria were burn injury affecting more than 15 % of the body surface and admission to our ward within 6 hours after injury. Exclusion criteria were electrical injury, presence of any obvious bacterial infection on admission,

extreme burn severity (>80% total burnt surface area), previously documented chronic left heart or renal insufficiency, age less than 18 years or documented previous medication affecting the inflammatory response of the body to burns (e.g. chronic use of corticosteroid medication) and known malignant disease. Burned patients did not receive medications, which considered affecting the inflammatory response-like corticosteroids-during the trial. The fluid therapy of our patients was guided by invasive transcardiopulmonary haemodynamic monitoring (PiCCO, Pulsion Medical Systems, Munich, Germany) <sup>22-24</sup>. Excision and grafting were started within 72 hours and enteral feeding was commenced on the first day after injury when haemodynamic stability was reached. 20-30% burned surface was excised and grafted in one sitting. Operations were repeated every 3-4 days. In case of suspected long-term ventilation tracheostomy was performed before the first grafting in order to avoid complications due to coagulopathy. If inhalation injury was suspected (facial burn, soot in the throat, chest X-ray) bronchoscopy was carried out for verification. Blood samples were taken on admission (day 1) and on the five consecutive days (days 2-6) at seven o'clock a. m. before operations or painful dressing changes. Six day study interval has been chosen because we had 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.

#### *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-9 and TIMP-1 were determined by the quantitative sandwich enzyme-linked immunosorbent assay (ELISA) techniques according to the manufacturer's instructions (R&D Systems Inc., Minneapolis, MN, USA). In comparison with standard MMP and TIMP curves, the concentrations of MMP and TIMP in plasma were determined spectrophotometrically (Multiskan Ascent microplate photometer, Type: 354, Thermo Electron Corporation, Waltham, MA USA) by reading the absorbance at 450 nm, and were expressed as entire amounts in the plasma (ng/ml).

### *Statistical analysis*

Statistical Package for the Social Sciences (SPSS) Statistics software, version 21.0 (IBM Corporation, USA) was used for statistical analysis. Data were expressed as median and inter-quartile range (IQR (standard 25th-75th percentile and 5th and 95th confidence interval) since their distribution was not normal by Kolmogorov-Smirnov test. Kruskal-Wallis test was used for intergroup analysis and survivors to non-survivors and patients to healthy controls were compared with Mann Whitney U test. Jonckheere-Terpstra test was used to detect significant trends. Correlations were analyzed with Spearman test. Values of  $p < 0.05$  were considered significant.

### **Results**

31 patients were involved in the study. 14 patients survived, 17 deceased. Demographic and clinical data are summarized in Table 1. We realized significant difference regarding age and extent of burn between survivors and non-survivors. By burns in general, the most frequent complications are sepsis, 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. No correlations were detected between enzyme levels and common severity scores (MODS, SOFA, SAPS II) on admission, but ABSI positively correlated with admission MMP-9/TIMP-1 ratios ( $r=0.454$ ,  $p=0.01$ ).

#### *Burned patients vs. controls:*

MMP-9 levels on admission and day 2 were significantly higher in burned patients than in healthy volunteers whereas MMP-9 levels on days 4-6 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 2-6 compared to admission levels (Fig. 1a).

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 2-6. 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).

MMP-9/TIMP-1 ratios were significantly higher in burned patients compared to healthy volunteers on admission and significantly lower on days 3-6. MMP-9/TIMP-1 ratio decreased continuously ( $p<0.001$ ) (Fig. 1c).

MMP-9 on admission showed a weak positive significant correlation with the extent of burns ( $r=0.437$ ,  $p=0.014$ ) (Fig. 1d). TIMP-1 did not show any correlation with the extent of burn injury (data not shown). MMP-9/TIMP-1 ratio presented a weak significant correlation with the burned surface area on admission ( $r=0.399$ ,  $p=0.032$ ).

#### *Survivors vs. non-survivors:*

MMP-9 did not show any significant difference between survivors and non-survivors (Fig. 2a). TIMP-1 presented a divergent tendency from day 4. TIMP-1 on days 5-6 showed weak significant correlation with survival (day 5,  $r=0.432$ ,  $p=0.028$ ; day 6,  $r=0.444$ ,  $p=0.014$ ). Comparing survivors to non-survivors the difference was significant on days 5 and 6 with higher levels in non-survivors (Fig. 2b). MMP-9/TIMP-1 ratio did not differ significantly between groups during the whole study period (Fig. 2c).

## **Discussion**

SIRS is frequently observed after thermal injuries and could be ended up with sepsis which is a feared and commonly fatal complication in burns. MMP-9 and TIMP-1 are considered important inflammatory regulators and signaling proteases. The role of MMPs and TIMPs in wound repair has been well studied, but little attention has been given to the circulating MMP and TIMP levels in burn and related SIRS. We aimed therefore to elucidate this missing point. However, before detailed

discussion the following limitations should be considered. Our results are monocentric and gained during retrospective analysis of a previous cohort. Burn and control groups are small in size. Interventions (dressing, grafting) performed during the trial period might influence our results.

In contrast to our study, Dasu and associates found elevated MMP-9 levels on day 21 only in children after thermal injury<sup>20</sup>. The underlying cause of the difference between the results may be the fact that patients were enrolled 48 hours after injury whereas in our study the first sample was taken within 8 hours after the injury. This difference might have been responsible for finding only a late elevation of circulating MMP-9 levels in that study, as in contrast we realized elevated levels in the first 48 hours. The early elevation observed in our study is new information to our knowledge and it suggests that MMP-9 may be a measure of skin damage. This suggestion is supported by our result like positive correlation was found between MMP-9 and burned body surface. In both studies elevation of TIMP-1 serum levels have been observed, but we also noted an earlier elevation. Stricklin and associates found similar results in a previous study regarding TIMP-1 levels in burn wound<sup>25</sup>.

SIRS also frequently associates to multiple injuries. Brumann and colleagues found the highest MMP-9 levels immediately after admission in polytrauma casualties, whereas TIMP-1 were increased significantly during the whole 72 hours study period after a low admission level<sup>26</sup>. These enzyme concentration kinetics are in concordance with our results. However, regarding injury severity and survival they realized no significant differences in contrast to our results. Lack of correlations in Brumann study might be due to short study period and small number of non-survivors.

Another study group of our institute found characteristic changes in septic patients, namely MMP-9 and TIMP-1 levels were elevated on admission and showed decreasing tendency<sup>16</sup>. In accordance with septic plasma MMP-9 characteristic, we noted elevation on admission and decreasing levels later on in burns. Contrary to septic results<sup>16</sup> by TIMP-1 we realized no difference at admission between the study and the control groups, but TIMP-1 increased in tendency until day 3 and remained elevated later on. The difference between the results obtained in septic and burned patients might be explained by the different time course of pathophysiological changes. The relationship between SIRS

and sepsis regarding time should be considered as a continuum. Trauma (burn, multiple injuries, ischemic-reperfusion phenomenon) is associated with up-regulation of pro-inflammatory mediators (TNF- $\alpha$ , IL-8), which are responsible for MMP-9 production<sup>27</sup> and SIRS generation. Later on SIRS could be ended up with sepsis. We experienced no septic complications by our study group during the trial period by the evaluation of clinical and laboratory parameters. Sepsis developed later on by our patients. Therefore, our study population could represent the post-injury SIRS period well.

Johnson and associates reported TIMP-1 elevation more than 60 hours before clinical sepsis. However, they - in concordance with our results - realized dissociation between TIMP-1 and MMP-9, which might suggest alternative activation and functions in SIRS patients who subsequently convert to sepsis<sup>28</sup>. Recent multicentric analysis reported association between increased admission TIMP-1 and mortality by septic patients<sup>14</sup>. Aforementioned results and our findings support the hypothesis, that each phase has own MMP-TIMP plasma characteristic. In the early post-injury period elevated MMP-9 and normal TIMP-1 could be realized. Later on in SIRS MMP-9 decrease, whereas TIMP-1 increase. Finally, if sepsis occurs, MMP-9 will be normal or near normal, while TIMP-1 will be increased. TIMP-1 above a certain cut-off level associates with bad outcome<sup>14</sup>. Therefore, late difference between survivors and non-survivors regarding TIMP-1 in our study might be the sign of later developing sepsis.

Time of sampling therefore has strong influence on measured MMP-9 and TIMP-1 plasma concentrations regarding SIRS and sepsis. So, time courses should also be considered during study planning in this field.

Prognostic value of scores (ABSI, Baux, etc.) and biomarkers are still a matter of intense debate regarding burn injury. We noted correlation between ABSI and MMP-9/TIMP-1, which might be due to the also realized correlation between MMP-9/TIMP-1 and the extent of burn. Further evaluation of MMP-9-TIMP-1 system in burn injury might contribute to develop new and better prognostic systems. Furthermore, TIMP-1 might be considered a marker of upcoming sepsis, which

might help to decrease mortality through early diagnosis.

## Conclusion

Current work is the first follow-up study regarding MMP-9 and TIMP-1 in burns. Dynamic changes could be observed especially in the first 72 hours and possibly due to the common SIRS related “cytokine storm”. Alteration of MMP-9-TIMP-1 system might influence SIRS and related mortality in burns. However, MMP-9 might be an injury marker of the future in burns after an extensive study.

## Acknowledgements

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## Legends for figures

**Figure 1.:** Plasma levels of **(a)** MMP-9, **(b)** TIMP-1, **(c)** MMP-9/TIMP-1 ratio in the control and in the patient groups. Data are expressed as minimum, maximum, median and inter-quartile range (IQR (standard 25th-75th percentile and 5th and 95th confidence interval)). Shaded boxes represent burnt patients, white boxes show healthy control results. The „#” symbols show significant differences ( $p < 0.05$ ) in burned patients compared to controls. (# =  $p < 0.05$ , ## =  $p < 0.01$ , ### =  $p < 0.001$ ). Asterisks indicate statistical differences within the burned group compared to day 1. (\* =  $p < 0.05$ , \*\* =  $p < 0.01$ , \*\*\* =  $p < 0.001$ ). Part **d** shows the weak correlation between BBS and MMP-9 on admission. MMP-9= matrix metalloproteinase-9, TIMP-1= tissue inhibitor of metalloproteinase-1, BBS= burned body surface.

**Figure 2.:** Plasma levels of **(a)** MMP-9, **(b)** TIMP-1, **(c)** MMP-9/TIMP-1 ratio in survivor and non-survivor patients. Data are expressed as minimum, maximum, median and interquartile range (IQR (standard 25th-75th percentile and 5th and 95th confidence interval)). Shaded boxes represent non-survivors, white boxes show survivors results. Asterisks indicate statistical differences between

survivors and non-survivors. (\*=  $p < 0.05$ ). MMP-9= matrix metalloproteinase-9, TIMP-1= tissue inhibitor of metalloproteinase-1

**Table 1.:** Demographic and characteristic data of our study group.

n=number, %=percent, NS: non-significant, SOFA: Sequential Organ Failure Assessment, MODS: Multiple Organ Dysfunction Score, SAPS II: Simplified Acute Physiology Score II, ABSI: Abbreviated Burns Severity Index, ICU: Intensive Care Unit

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**Table 1.**

|                         | All patients<br>(n=31) | Survivors (n=14) | Non-survivors (n=17) | p value |
|-------------------------|------------------------|------------------|----------------------|---------|
| Age (years)             | 51 (37-71)             | 44 (30-56)       | 58 (46-74)           | p<0.05  |
| Burned surface area (%) | 30 (20-50)             | 24 (18-33)       | 40 (30-55)           | p<0.01  |
| Deep burn injury (%)    | 27 (18-35)             | 20 (15-25)       | 30 (27-40)           | NS      |
| Inhalation injury (n)   | 9                      | 4                | 5                    | NS      |
| Flame burn injury (n)   | 11                     | 7                | 4                    | NS      |
| Blast burn injury (n)   | 6                      | 4                | 2                    | NS      |
| Scald burn injury (n)   | 5                      | 3                | 2                    | NS      |
| SOFA score              | 7 (5-9)                | 7 (5-10)         | 7 (5-8)              | NS      |
| MODS                    | 5 (3-6)                | 5 (4-7)          | 6 (3-6)              | NS      |
| SAPS II                 | 31 (24-43)             | 27 (24-40)       | 34 (27-45)           | NS      |
| ABSI                    | 8 (7-9)                | 8 (6-8)          | 8 (7-10)             | NS      |
| Renal failure (n)       | 10                     | 3                | 7                    | NS      |
| Hemodialysis (n)        | 10                     | 3                | 7                    | NS      |
| ICU stay (days)         | 10 (7-20)              | 10 (7-21)        | 10 (7-22)            | NS      |

Figure 1

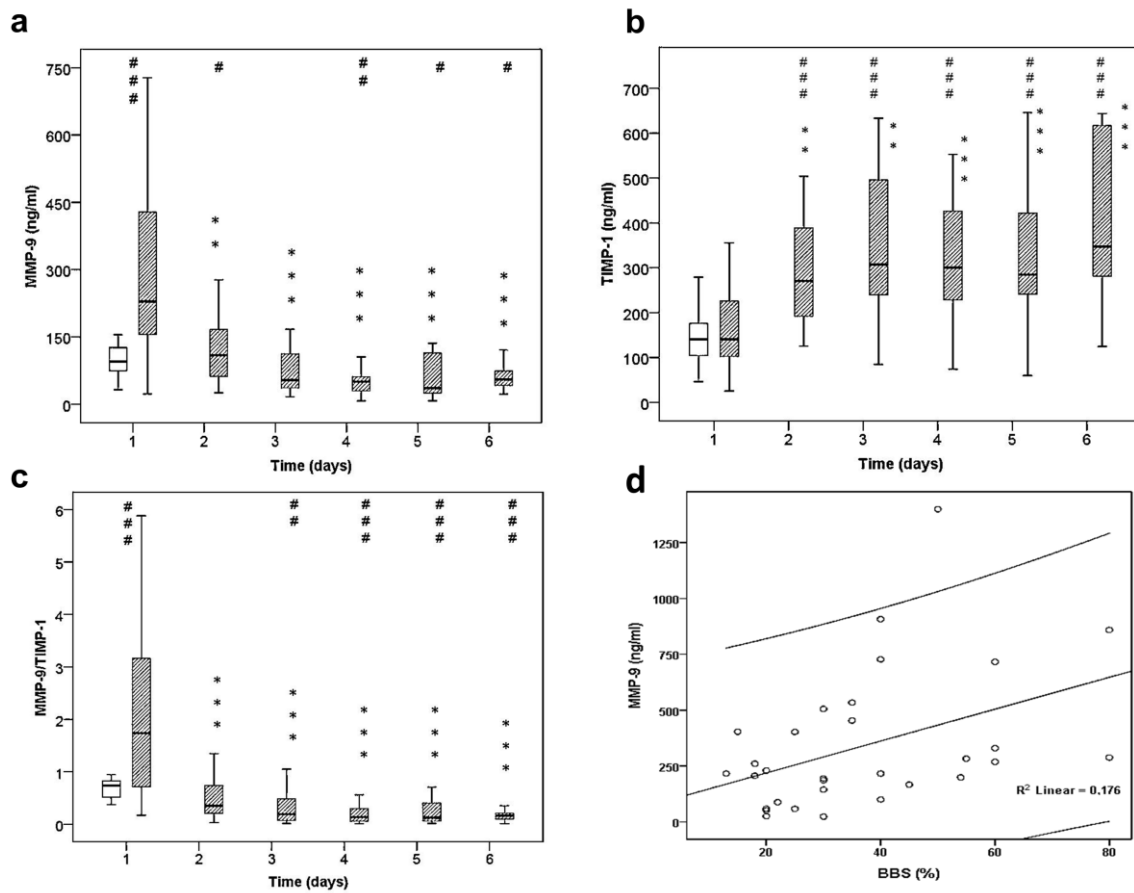
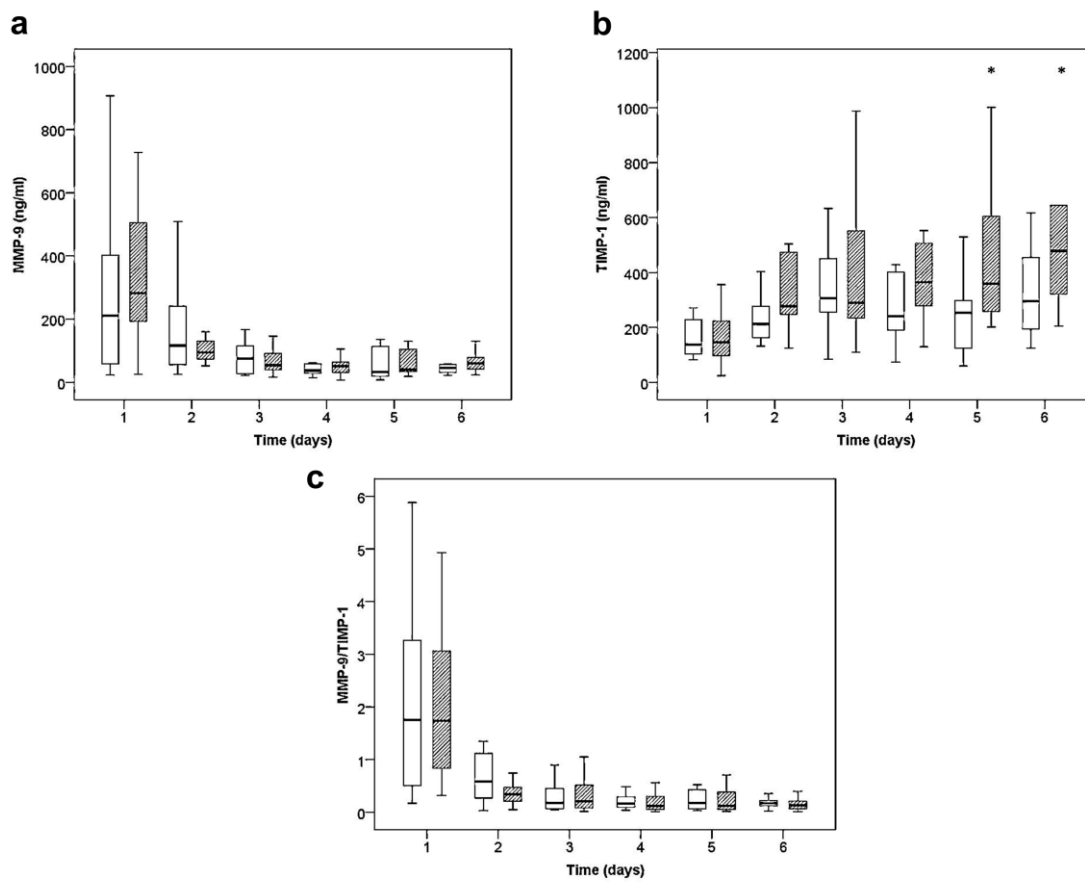


Figure 2



**Highlights:**

1. First follow-up study regarding MMP-9 – TIMP-1 system in severe burns.
2. Dynamic changes could be observed especially in the first 72 hours.
3. MMP-9 was significantly higher on admission in burns, than decreased in tendency.
4. TIMP-1 increased during the trial and correlated with survival at days 5 and 6.
5. MMP-9 correlated with the extent of burn and might be an injury marker.