SELENIUM AND SELENOPROTEIN P DEFICIENCY CORRELATES WITH COMPLICATIONS AND ADVERSE OUTCOME AFTER MAJOR TRAUMA

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ABSTRACT—**Background:** A declining selenium (Se) status constitutes a characteristic of critical illness and may affect disease course and survival. The dynamics of trauma-induced changes in biomarkers of Se status are poorly characterized, and an association with multiple organ failure (MOF) and mortality can be hypothesized. It was the aim of this study to investigate Se and selenoprotein P (SELENOP) concentrations in major trauma patients during the early posttraumatic period. **Patients and Methods:** Twenty-four patients after major trauma (ISS ≥16) were included at our level one trauma center. Se supplementation ever during the 90-day observation period was defined as an exclusion criterion. Serum samples were drawn within less than 60 min after trauma, and after 6 h, 12 h, 24 h, 48 h, and 72 h. Serum Se was analyzed by X-ray fluorescence and SELENOP concentrations by ELISA. The data were correlated to clinical parameters, occurrence of MOF defined by MOF and APACHE II score, lung injury defined by Horowitz index and clinical outcome (90-days survival). **Results:** Serum Se and SELENOP concentrations of the trauma patients were significantly below the average of healthy European subjects (mean ±SD; Se, 41.2±8.1 vs. 84.7±23.3 μg/L, $P < 0.001$; SePP, 1.5±0.3 vs. 4.3±1.0 mg/L, $P < 0.001$). A strong deficit was present already at the first time point (Se; 33.6±10.5 μg/L, SELENOP: 1.4±0.5 mg/L). The clinical scores collectively showed an inverse relation between health status and Se biomarkers. Patients who did not survive the 90-day observation period exhibited significantly lower initial post-trauma Se status than the surviving patients (mean±SD; Se, 24.7±7.2 vs. 39.2±8.4 μg/L, $P<0.05$; SePP, 1.1±0.4 vs. 1.6±0.4 mg/L, $P<0.05$). **Conclusion:** Very low Se and SELENOP concentrations occur fast after major trauma and are associated with poor survival odds. These findings support the notion that early Se substitution may constitute a meaningful adjuvant treatment strategy in trauma patients.

KEYWORDS—APACHE II, major trauma, MOF, selenium, SELENOP, SIRS

INTRODUCTION

Severe trauma induces a complex systemic immune response with a substantial impact on posttraumatic survival. In contrast to earlier theories of a sequent post-traumatic immune reaction starting with a state of hyper-inflammation (systemic immune response syndrome [SIRS]) followed by a compensatory anti-inflammatory immune response (1), recent hypotheses propose that both SIRS and CARS occur simultaneously even in the initial phase after injury (2). The development of multiple organ dysfunction or even failure (MOF) is the result of the intensity and balance of these opposing trauma-induced inflammatory immune reactions, causing high-mortality rates among critically ill patients (3).

In this context, some authors have examined the roles of serum selenium (Se) and found its deficiency to be associated with systemic inflammatory response syndrome and sepsis. Further, selenoprotein P (SELENOP) biosynthesis and concentrations have been shown to decrease in sepsis potentially causing the decline in Se levels (4, 5). However, the dynamics of decreasing serum Se and SELENOP concentrations and their relation to the pathophysiology and outcomes in critical ill and major trauma are not well characterized. In contrast to investigations of selenium in sepsis, definition of onset in major trauma is clear. Therefore, the overall objective of this study was to investigate serum Se and SELENOP levels in critically injured patients at an initial post-trauma time point starting already within 60 min after the injury, and to correlate Se and SELENOP concentrations to distinct clinical outcome parameters like the development of MOF, traumatic lung injury, and 90-day survival.

PATIENTS AND METHODS

Patients

This study was performed in our level one trauma center strictly according to the Good Clinical Practice Guidelines. The Ethical Committee

of Ludwig Maximilian University of Munich (LMU) approved and certified the study by the local institutional review board (reference number: AZ 012-00). Patients over the age of 18 years suffering from blunt multiple injuries with an Injury Severity Score (ISS) $\geq$ 16 who were admitted to our emergency department within 60 min after trauma were included. Consent form of study participation was obtained from the patients or a legal representative.

Patients presenting with isolated traumatic brain injury, malign or infectious disease and patients under immunosuppressive therapy were excluded. Further, patients who were supplemented with Se within 72 h after trauma were excluded, as Se supplementation during ICU stay did not follow a stringent protocol. Patients' treatment was performed according to standard of care and was not affected by study participation. The biomarkers were analyzed and compared with MOF scores, APACHE II score, the severity of lung injury as measured by the Horowitz P/F ratios, and 90-day survival rates. Multiple organ failure was assessed using MOF score as modified by Lefering et al. (6). Classification according to severity of disease was achieved on the basis of the median value of the "Acute Physiology and Chronic Health II" (APACHE II) score (7), and according to lung function and extent of traumatic induced lung damage by the median Horowitz index. Serum Se and SELENOP concentrations of the trauma patients were compared to average healthy European subjects from a cross-sectional investigation analyzed recently in the so-called EPIC study (8).

Blood sampling

Blood samples were drawn within the first 60 min after trauma on admission ("1h"), and again at 6 h, 12 h, 24 h, 48 h, and 72 h. Sampling time points were strictly standardized to the traumatic event. Afterward, samples were stored at −80°C until analysis.

Assays

Serum Se concentrations were determined by total reflection X-ray fluorescence (TXRF) analysis using a benchtop TXRF analyzer (S2 Picofox, Bruker Nano GmbH, Berlin, Germany) as described (9). SELENOP concentrations were measured by a validated ELISA (10). The two Se status biomarkers were analyzed in a research lab remote from the study center and by personnel blinded to the sample identities. Assay characteristics, test performance, and validation procedures were as described (8).

Statistical analysis

Statistical analyses were performed using SPSS Statistics Version 25.0 (IBM Corporation, Armonk, NY) or Graph-Pad Prism (version 5; GraphPad Software Inc). The association of serum Se and SELENOP concentrations at the different time points post trauma was analyzed by linear regression. To take sequential measurements into account and evaluate protein dynamics in particular, a statistical model for repeated measures analyses (repeated measures MANOVA, SPSS General Linear Model) was chosen. The following parameters were included in the model: time to indicate significant protein dynamics, development of organ failure detected by MOF score, APACHE II score, Horowitz index, and 90-day survival. Groups were divided according to distinct clinical parameters (MOF, APACHE II, Horowitz index, 90-day survival). Patients were allocated to dichotomous groups depending on the median values. If findings were statistically significant, the single points in time were secondarily evaluated using non-parametric Mann–Whitney U test. All values according to the clinical data are given as mean ± SD, Se levels as μg/L, and SELENOP levels as mg/L.

RESULTS

Patients

Sixty patients were screened for inclusion into this prospective study. Due to incomplete data sets and Se supplementation within the first 72 h after trauma, respectively, 36 patients had to be excluded, and 24 patients fulfilled all inclusion criteria (age range: 42.3 ± 15.6 years (23−94); sex ratio: 42% female). Mean (range) ISS of all patients was 43 ± 14 (21−75), and mean APACHE II score was 16 ± 7 (5−34). The MOF score was 4.2 ± 1.5 at the first time point of analysis (1 h), and 4.0 ± 1.4 after 72 h (maximal MOF 5.6 ± 0.9). Mean Horowitz index was 370.5 ± 210.2 at 1 h and 316.6 ± 110.9 at 72 h after

trauma. Eight patients did not survive the observation period, i.e., until 90 days after trauma (36%). Patients who died within the observation period showed significantly higher APACHE II scores ($P<0.0001$), significantly lower Horowitz-indexes after 1 h ($P<0.001$) and significantly lower minimal Horowitz-indexes ($P=0.001$). Patients received 11.2 ± 13.2 RBC units, 13.5 ± 15.8 FFP units, and 1.8 ± 2.7 thrombocyte units during the observation period. Detailed clinical data are given in supplemental Table 1, http://links. lww.com/SHK/A863.

Alterations of Se status biomarkers in serum

Selenium—Serum Se levels were significantly lower at all the time points analyzed in the trauma patients as compared with a large cohort of healthy European adults (Fig. 1A). The serum Se concentrations were minimal at the initial time point analyzed, i.e., within the first 60 min after trauma. On average, Se concentrations increased during the next hours, reaching a relative maximum after 12 h, and then declined again. At all time points of analysis, serum Se concentrations were far below normal levels (Fig. 1A). There were no significant differences regarding Se status between women and men in this cohort (not shown).

Selenoprotein P—The dynamic changes of serum SELE-NOP levels within the first 72 h after major trauma are qualitatively similar to the alterations observed in serum Se.
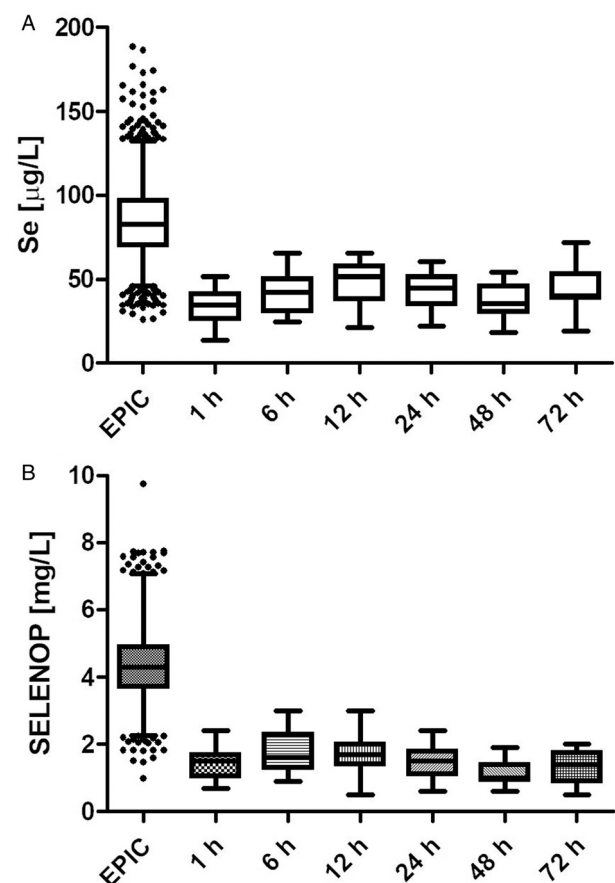

Fig. 1. **Normal range—according to the "Epic study," (8) and time course of total serum Se and selenoprotein P in all patients.**
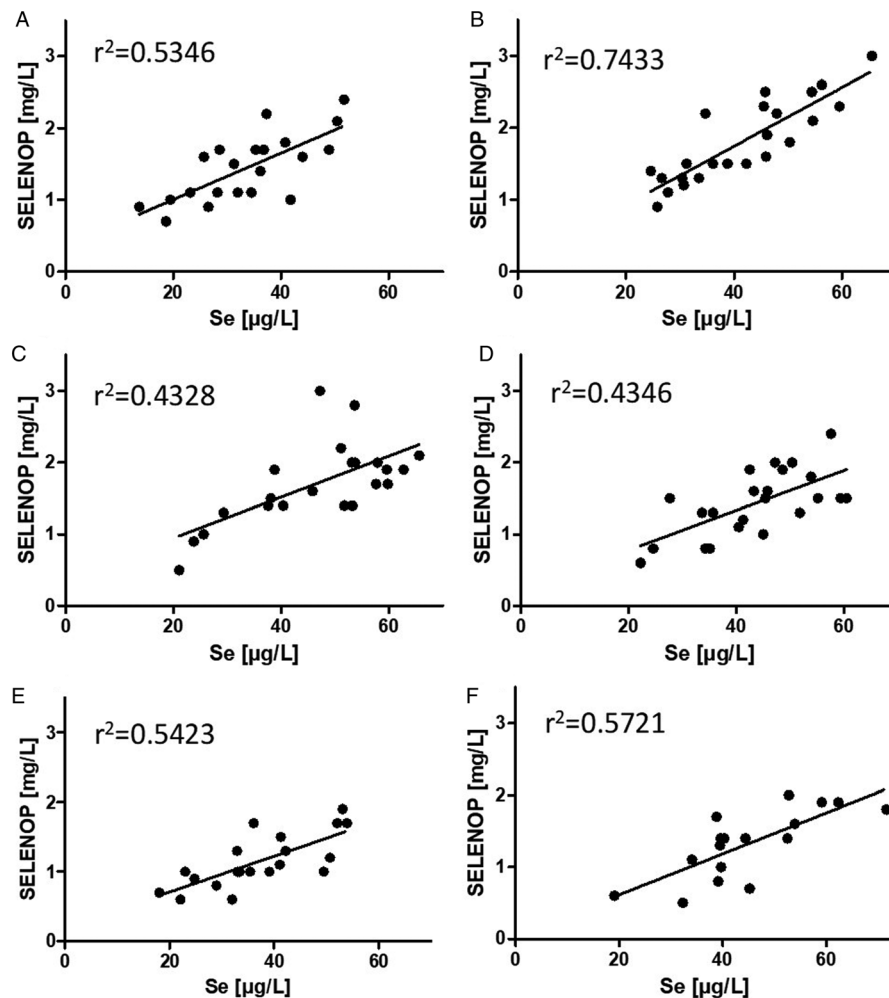
FIG. 2. **Linear regression of SE and SELENOP: (A) 1 h, (B) 6 h, (C) 12 h, (D) 24 h, (E) 48 h, (F) 72 h.**

SELENOP concentrations were also very low at the first time point of analysis, i.e., at 1 h after the traumatic event (Fig. 1B). A relative maximum of SELENOP concentrations is observed 6 to 12 h after trauma.

Correlation of serum Se and SELENOP concentrations after trauma

Healthy subjects with insufficient Se intake show a tight correlation of serum Se and SELENOP concentrations, which is not observed in subjects with a high Se status where selenoprotein biosynthesis has become independent of further intake (4).

Regulation of selenium

In linear regression analyses, the trauma patients display a relatively tight correlation between serum Se and SELENOP concentrations at all the time points analyzed, indicating a relative Se deficit (Fig. 2). An exceptionally high correlation of $r^2 = 0.7433$ is observed at the 6 h time point, which coincides with the relative maximum of serum Se and SELENOP concentrations during the time period under analysis (Fig. 2B). This value is higher than the correlation coefficient determined for the recently analyzed cohort of healthy European adults ($r^2 = 0.3227$), who displayed a

much higher average Se and SELENOP concentration range (Fig. 1, A and B).

Relation of serum Se biomarkers to 90-day survival

The concentrations of serum Se and SELENOP of the patients who survived and the ones who died show a different pattern of changes. The group of surviving patients displayed on average a relatively constant serum Se and SELENOP status (Fig. 3, A and C). The concentrations of the two Se biomarkers are altered in the group of non-surviving patients in a more dynamic pattern, displaying a relative maximum at 12 h and 6 to 12 h after trauma, respectively (Fig. 3, B and D). The initial Se and SELENOP concentrations differ significantly in relation to survival, and the patients who died showed both lower Se and lower SELENOP concentrations as compared with the surviving patients (Fig. 3, E and F).

Relation of serum Se biomarkers to the clinical parameters

Multiple organ failure (MOF)—Patients were categorized into two groups according to the median MOF score of 6. MANOVA analysis revealed a time-dependent difference of serum SELENOP concentration changes within the first 72 h
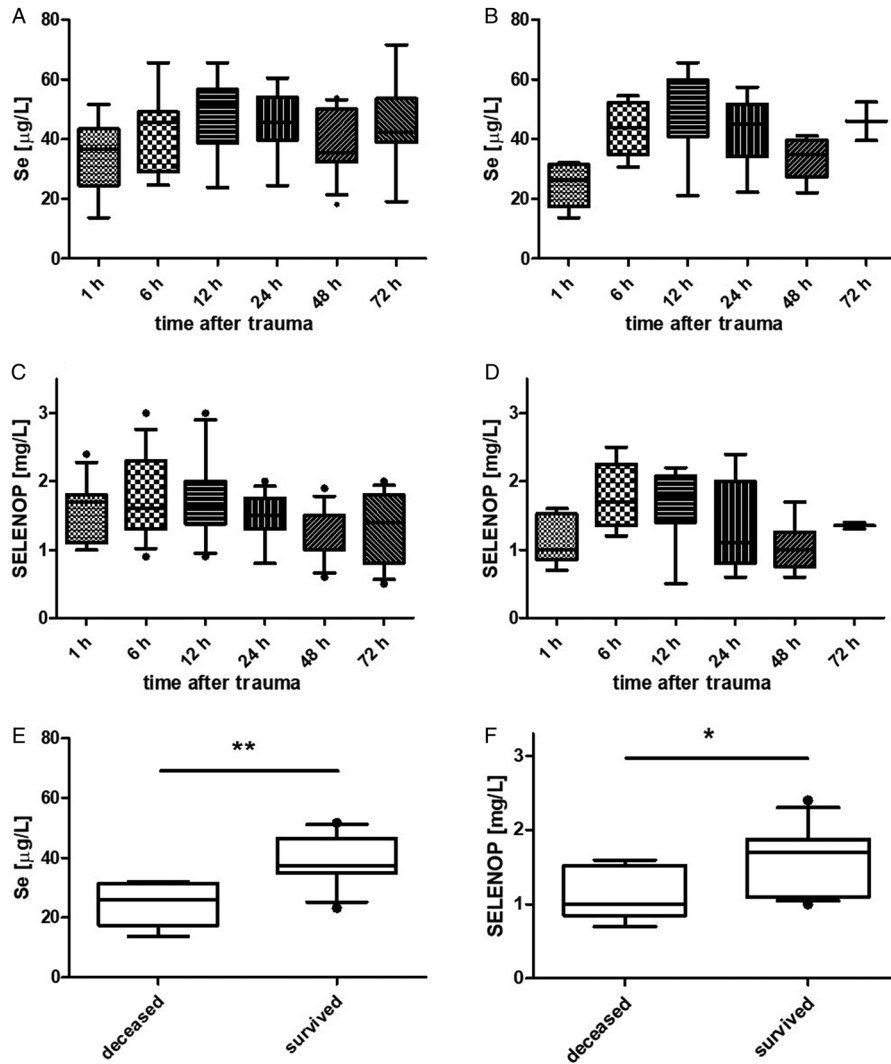
FIG. 3. **Survival 3 months, Mann–Whitney rank sum test: all time points: (A) surv, (B) died, (C) surv, (D) died, Se and SELENOP at 1 h (E, F).**
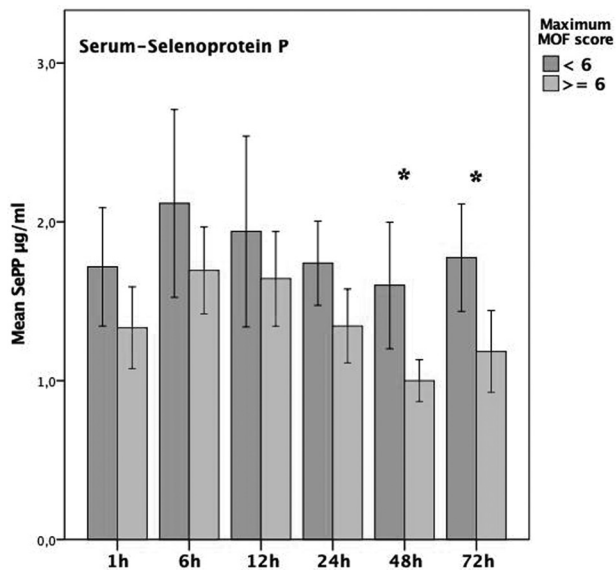

FIG. 4. **MANOVA analysis and *t* test for SE and SELENOP depending on MOF score.**

after trauma with respect to suffering or not from MOF (Fig. 4, $P < 0.001$). MOF-positive patients showed significantly lower SELENOP levels at all the time points than those presenting with a MOF score < 6 (MANOVA; $P = 0.018$). This interaction was not observed for serum Se concentrations (not shown). *T* test was performed to evaluate Se and SELENOP differences at the single time points depending on MOF score. Statistically significant differences were observed after 6 h for Se ($P = 0.046$), and after 48 h and 72 h for SELENOP ($P < 0.001$ and $P = 0.024$, respectively). Regression analysis did not indicate a significant correlation between the development of a MOF and the immediate ($t = 1$ h) serum Se or SELENOP concentration.

APACHE II score—Patients were categorized into two groups according to the median APACHE II threshold score of 15 (APACHE II < 15; APACHE II ≥ 15). MANOVA analysis indicated significant differences in serum Se ($P = 0.007$) and SELENOP ($P = 0.001$) concentrations within the first 72 h after major trauma in both groups. *T* test was performed to evaluate Se and SELENOP levels at the single time points depending on APACHE II score. Significantly different serum
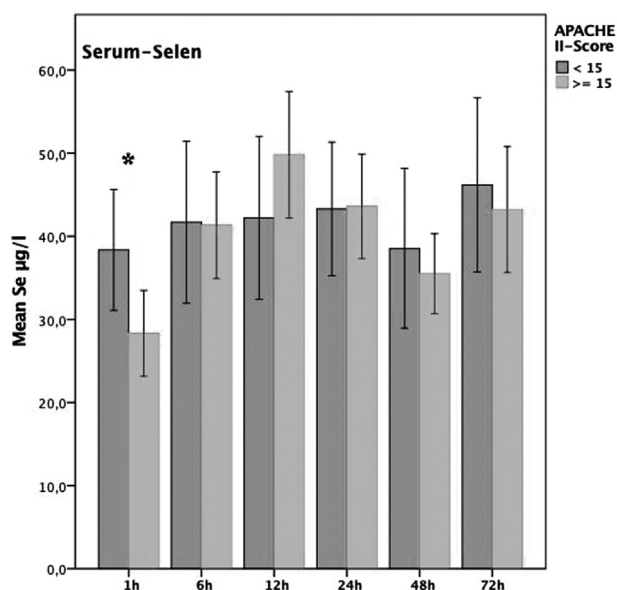
FIG. 5.   **MANOVA analysis and *t* test for SE and SELENOP depending on APACHE II score.**

Se concentrations were observed immediately after trauma, i.e., at the 1 h time point (Fig. 5).

Horowitz index—Patients were separated into two groups according to the median Horowitz index of 242 as threshold value (Horowitz<242 vs. Horowitz≥242). Serum SELENOP concentrations showed significant time-dependent alterations within the 72 h after trauma in both groups (MANOVA; $P<0.001$). Serum Se and SELENOP levels were lower in the group of patients presenting with the poor Horowitz indexes as compared with the other group. *Post hoc* testing using *t* test demonstrated significantly different serum Se levels at 48 h after trauma ($P=0.036$, data not shown). There were no statistically significant differences in the SELENOP concentrations between the two groups (not shown).

DISCUSSION

In this study, we prospectively evaluated the Se status in patients after multiple major trauma, starting within 60 min after the injury (denoted as t = 1 h). To assess the Se status, serum levels of two important biomarkers, i.e., total serum Se and the Se transport protein SELENOP were measured (11). Our data indicate that both biomarkers are affected in a similar manner, displaying a comparable dynamic response to the traumatic injury. To our surprise, both biomarkers of Se status were already extremely low at the initial time point of analysis, i.e., within the first 60 min after the traumatic event. This finding indicates that drastic changes in serum Se and selenoprotein concentrations must have taken place immediately in response to the injury. This result is in contrast to the low Se status observed in sepsis, where a more gradual and slow decline of the Se biomarkers is observed and a major role of declining hepatic selenoprotein

biosynthesis and SELENOP secretion is discussed (12). Moreover, a predisposition of subjects with low Se status to a higher infection risk and severe disease development is assumed in sepsis (5). This explanation cannot be applied to the patients with major trauma, as no such predisposition to the injury can be made responsible for the drastic Se deficits observed in this study. Collectively, our findings support the assumption of a very fast and strong modulation of SELENOP distribution and uptake into or association with the target cells immediately in response to the traumatic injury.

The relatively high correlation coefficients between serum Se and SELENOP argue in favor of SELENOP-specific pathways causing a selective removal of the Se transporter from the circulation. It remains to be determined whether this effect is mediated via SELENOP-specific receptors on Se-target cells (13) or via less-selective interactions of SELE-NOP with regular membrane components like heparin in the extracellular matrix of injured tissue (14). Conversely, the very high correlation coefficient between serum Se and SELENOP concentrations during the phase of increasing Se status at 6 h after injury may be interpreted as an indication of increased SELENOP biosynthesis dominating serum Se concentration changes during the immediate response to the injury. If this assumption is strengthened by follow-up analyses, it might offer some explanation to the previously observed beneficial effects of supplemental Se in critical illness (15), as some extra Se might efficiently support SELENOP biosynthesis during the first hours after the traumatic injury. Notably, our data indicate an association of the degree of Se deficit in polytrauma patients with a number of clinical markers of critical illness including the APACHE II, Horovitz, and MOF indices, collectively reflecting disease severity and survival odds.

Several studies have shown that severe injury and oxidative stress trigger the development of systemic inflammatory response syndrome. Intracellular oxidative imbalances result in mitochondrial dysfunction and enhance the production of reactive oxygen species (ROS) (16).

A sufficiently high Se status is essentially needed for biosynthesis of the glutathione peroxidases (GPX), thiore-doxin reductases (TXNRD), and other selenoproteins implicated in the antioxidative defense, thereby enabling an adequate physiologic response (16). Several authors have described an inverse correlation of Se levels and critically illness (17). Patients suffering from systemic immune response syndrome or sepsis following trauma or burn show significantly depressed serum Se and GPX activity levels. These results suggest that serum Se decline is associated with elevated ROS production and inflammatory response (18). Platelets are also known to contain high Se levels (19). Major trauma is typically associated with relevant bleeding and platelet consumption, which can be another cause for the fast Se deficiency observed early after trauma. Despite pathological low Se and SELENOP levels in our study patients, we identified further clinical conditions that are associated with low Se status.

Severity of illness (MOF/APACHE II)

A major finding of this study is that critically ill trauma patients scored by APACHE II >15 measured significantly lower Se concentration levels immediately—which means no later than 60 min after trauma. The correlation between serum Se levels after 1 h and APACHE II score is very significant. Regression analysis between initial Se concentration and Apache II count is also highly significant. The latter has been described as a reliable prognostic factor for survival or not in major trauma patients (20). These and our results postulate initial low Se concentrations after major trauma as a strong risk factor for further complications. Decades before, von Gagern et al. (21) already described diminished Se levels after major trauma, the study design differs from ours as the first blood sample was taken sometime on day 1 (and follow up), but not as early as ours. Knowing that Se deficiency is a phenomenon of the initial post trauma phase supports the idea of an early Se substitution. SELENOP plays a key role in Se storage and transport (4). In our setting, not only Se but also SELENOP was reduced in patients with distinct MOF. Dysfunction in microcirculation and thereby deranged organ perfusion are important triggers of MOF. SELENOP reduces phospholipid-hydroperoxides and thereby protects endothelial cells from oxidative stress and consecutive disturbances in microcirculation (22).

Acute lung injury—The lungs are the organ first and most commonly involved in MODS after severe trauma. Acute respiratory distress syndrome (23) that is caused by acute lung injury after trauma is a critical component of MODS. Following severe trauma, trace element (TE) levels in the lungs are significantly altered. Patients with severe lung injury presented by critical Horowitz indices had lower levels of Se and SELENOP at all time points by trend, at 48 h the differences are significant. Previous studies identified extensive PMN infiltration and activation as to be an important trigger for ARDS following acute lung injury. PMN overload leads to an excessive flush of cytokines and pro-inflammatory mediators. As ICAM-1 plays a significant role in leucocyte adhesion to endothelial cells, it may also indicate secondary lung injury (24). Wang et al found a faster raise but earlier drop of ICAM-1 in TE supplemented animals after lung injury, which indicates that Se may limit ICAM-1 overflow. Another potentially protective mechanism of Se and selenoproteins may inhibit NFκB activity thereby leading to the reduction of ICAM-1 and other pro-inflammatory agents (25).

Survival and potential therapeutic implications—In accordance with our findings, Manzanares et al. (26) also demonstrated that plasma Se deficiency was associated with higher mortality in critically ill patients. Major strength of our study is the identification of a very early Se deficit following major trauma. Almost all studies that have investigated the immune response to trauma have analyzed blood samples acquired in a later time frame after hospital admission. Thus, we know little of the immune status of patients in the immediate post injury phase and how this might influence patient outcomes. This very early detectable lack of Se and potential negative influence on

the further clinical course constitutes a most valuable information considering supplementation.

Berger et al. (27) reported in their intervention study that antioxidant supplementation (Se, zink, and glutathione) could reduce the extent of systemic inflammation but not early organ dysfunction in trauma patients and such after cardiac surgery. Selenium substitution in patients with severe septic shock seems to improve the clinical course and reduces mortality rates (15). Khalili et al. found significantly better neurological outcome in patients with severe traumatic brain injury after Se substitution (15). Despite these early and promising results Langlois et al. (28) critically discuss the widespread use of Se substitution in intensive care in their recent review. They point out that there are still many open questions in defining deficiency, in substitution dose, and in clear clinical indications (28).

Our findings thereby may add another aspect to this discussion. Several other studies and our own investigations pinpointed that distinct changes in immune response and one step before—in gene expression of immune response associated proteins can be detected already at a very early stage after trauma (29). The present investigation clearly revealed very low Se levels in trauma patients already immediately after the traumatic event and thereby directly connects even lower Se levels to morbidity and mortality.

From our point, there are several possible causes of selenium and selenoprotein P deficiency in our cohort. First, it has well been documented that inflammation in general is associated with a lower selenium status. Following severe trauma, surgery, sepsis, and severe systemic inflammatory response concentrations of selenium significantly decrease. Serum Se has further been identified as a negative acute-phase reactant (30). Some authors propose that this reduction may deplete circulating antioxidants leading to an elevation of ROS thereby exacerbating the severity of illness (31). Other groups have also suggested that decreased plasma trace elements concentrations are associated with severity of critical illness (32). Moreover, inflammatory cytokines, namely IL1β, TNF-α, and INFγ, have been identified to significantly decrease promoter activity, suggesting a repression of SeP expression during acute phase reaction (33). Renko et al. have shown that hepatic Se metabolism becomes progressively disturbed during the acute phase reaction negatively affecting serum Se status by insufficient biosynthesis of Sepp1. As a result, regular Se metabolism and Se transport is severely interrupted (12). Hypoxia—as regularly associated with trauma-induced shock—has also been identified as an important stimulus to redirect selenoprotein biosynthesis leading to reduced selenoprotein P expression and thereby decreased selenium export from hepatocytes. Specifically, Becker et al. (34) could show that hypoxia reduces transcript concentrations of central components controlling selenium and selenocysteine metabolism. Furthermore, hypoxia is associated with a general decline of selenoprotein expression (34). Therefore, the detected selenium-dependent decline of SELENOP biosynthesis in case of hypoxia might be the reason for the progressive selenium deficit that is associated with severe diseases. In case of major

trauma these pathophysiological changes may explain the low selenium and SELENOP concentrations detected in our cohort of critically injured patients in the very early posttraumatic period.

LIMITATIONS

We are aware that our study has several limitations; one relevant limitation is the small patient count. We needed to exclude several patients because of Se supplementation some-time during ICU stay. As this did not follow strict standardization, we also were not able to retrospectively compare one group with and one group without supplementation, but rather had to exclude patients who received Se during the observation period (90 days after trauma). The substantially new information of the present study is that SE deficiency occurs strong and very early in these patients, already at 1 h after the trauma. We may need to think about very early supplementation to investigate on later benefits like reduced MOF or mortality rates in a randomized controlled trial.

Another potential bias is that trace element levels in critical patients were decreased by factors such as increased oxidative stress, use of anti-oxidant systems, hemodilution with fluid resuscitation, renal replacement therapies, losses in biological fluids, and inadequate intake. The patients in our study required resuscitation with blood components and crystalloids which may influence SE and SELENOP levels. As blood products from healthy donors also contain trace elements like SE, dilution effects are rather caused by crystalloid fluid resuscitation and less than by blood product resuscitation. However, even if these circumstances cause low plasma levels, the effect on the patients' immune system would be the same.

Furthermore, assorting patients according to APACHE II, lung injury by Horowitz quotient and finally outcome are connected to each other and cannot be strictly regarded separately. However, we consider that our data evaluation enables the identification of certain patient subgroups that are especially at risk for relevant Se deficit and may especially profit from substitution.

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