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The Fractional S100B Excretion is Attenuated Following Neurotrauma Suggesting an Innate Conservation System for Neurotrophic Proteins

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Abstract

Background/Objectives: S100B is a well-established neuromarker for cerebral damage, with renal elimination playing a key role in interpreting its serum levels. The aim of this study was to assess whether the renal S100B elimination is different in neurotrauma and control patients**.**

Methods. In a prospective single-center study, 129 patients were consecutively enrolled admitted to the intensive care unit either because of traumatic brain injury, subarachnoid hemorrhage, stroke (neurotrauma, n=54) or following elective extracranial surgery (control, n=75). Blood and urine samples were collected daily at 6AM. S100B levels were measured using the LIAISON® Sangtec®100 immunoanalyzer, and creatinine was determined enzymatically with the Advia 2400 Chemistry system. The fractional S100B excretion (FE_{S100B}) was calculated using the formula $C_{S100B(urine)}$*$C_{creatinine(serum)}$/$C_{S100B(serum)}$*$C_{creatinine(urine)}$.

Results. Neurotrauma patients were younger than controls (mean 66 vs. 69 years, p=.007) and suffered from less comorbidities (Charlson index 3 vs. 6, p=.009). S100B serum levels increased significantly after neurotrauma, peaking on day 3 and 4 (0.94±1.84µg/l, p=.028 and 0.86±1.67ug/l, p=.027) as compared to control patients. S100B urine levels were increased both in neurotrauma and control patients. The fractional S100B excretion was significantly attenuated on day 3 and 4 (0.18±0.27µg/l, p<.001 and 0.31±0.61ug/l, p=.045) following neurotrauma.

Conclusions. The 21kDa dimeric protein S100B is not fully reabsorbed by the kidneys after increased serum release, making urinary measurements a potential alternative for detecting elevated S100B levels. However, the attenuated renal elimination respectively enhanced reabsorption of S100B following neurotrauma may indicate a physiological mechanism to conserve neurotrophic proteins.

Keywords: Brain Injury, Biomarker; Neurotrauma; Renal Function; S100B

Introduction

Neuromarker comply with the desire for a simple indicator to determine the extent of neurotrauma, and to monitor the success of therapeutic interventions. S100B protein has been proposed in this role. Over the past decades, numerous studies reported a positive correlation between high S100B levels in blood ($S100B_{serum}$) or cerebrospinal fluid (CSF) and impaired neurological function following various types of Central Nervous System (CNS) injuries [1-4]. Furthermore, S100B measurements in urine ($S100B_{urine}$) have been demonstrated feasible in infants, children, and adults [5-9]. S100B is a low molecular weight (21 kDa) dimeric calcium-binding protein [10,11] that is most abundant in glial cells of the CNS [12]. Following in vitro injury, S100B release from astrocytes continues to increase up to 48 hours [13,14] while $S100B_{serum}$ levels in patients are highest directly after a brain injury and become normalized within 24 hours in most cases, even in those patients with a bad outcome [15]. Following human brain injury, an impaired S100B passage from CSF to blood correlates with a better neurological function suggesting an innate CNS conservation system for S100B thereby contributing to recovery [16]. The subsequent renal elimination of S100B was initially investigated following cardiac surgery, where increased $S100B_{serum}$ levels were attributed to an altered Blood-Brain-Barrier (BBB) [17,18]. Thereafter, the renal clearance of S100B was assessed in a porcine model of encephalopathy [19]. The present knowledge on the renal handling of physiologically relevant peptides or small proteins such as S100B in general is limited. Protein transport in the kidney was elucidated in the 1970ies [20]. The glomerular sieving has a cut-off around 60 kDa, based on albumin studies. But in addition to glomerular filtration, protein reabsorption has to be considered, which involves specific transporter systems [21,22]. For example, albumin (66kD) is reabsorbed by the proximal convoluted tubule (71%), the loop of Henle and distal tubule (23%), and collecting duct (3%), thus indicating that the kidney plays an important role in protein metabolism [23]. To determine the renal protein turn-over, an isolated urine sample does not have a great value unless a normalization of the urine protein to creatinine ratio is calculated. The National Kidney Foundation recommends the spot urine protein to creatinine ratio, instead of a 24 hour urine collection to diagnose proteinuria in most situations [24]. Following brain injury, the measurement of $S100B_{serum}$ poses the first choice since blood samples are readily available although CSF samples would reflect cerebral S100B concentrations more accurate. Interpreting $S100B_{serum}$ constitutes a dual challenge. Firstly, the contribution of extracerebral S100B sources remains unclear [25]. Secondly, renal S100B protein reabsorption emerges as a possibility. The purpose of the present prospective study was to compare the temporal profile of S100B release into blood and urine following neurotrauma as well as the respective renal S100B elimination.

Materials and Methods

The protocol of this study was approved by the Ethics Committee of the University Erlangen-Nürnberg (Re.-No. 3663, 22.08.2007) and was registered at ClinicalTrials.gov (NCT04501315). All procedures involving human participants were in accordance with the ethics standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethics standards. Informed written consent was given by the patient or the next-of-kin in each case. Exclusion criteria comprised those below 18 years of age, pregnancy or nursing state, expected to die within 48 hours, or melanoma.

Subjects

Patients were consecutively enrolled following admission to the intensive care unit. A total of 129 patients were enrolled, 54 neurotrauma patients (27 male, mean age 66 years with a range from 18 to 95 years) and 75 control patients (34 male, mean age of 69 years with a range from 36 to 91 years. Neurotrauma patients suffered from Traumatic Brain Injury (TBI) (mild n=11, moderate n=7, and severe n=10), stroke (n=17), aneurysmal subarachnoid hemorrhage (n=4), hydrocephalus (n=1), brain tumor (n=6) or spinal injuries (n=3). The control group comprised of elective abdominal surgery (n=37), orthopedic surgery (n=18), vascular surgery (n=11), urological (n=4) and gynecological (n=5) procedures. The Charlson Comorbidity Index (CCI) is an assessment tool specifically designed to predict long-term mortality [26]. A score of zero indicates that no comorbidities are present. The higher the score, the higher the predicted mortality rate. For all patients, both neurotrauma and control groups, the CCI grades were determined. The majority of neurotrauma patients had a score of 0 (n=18, 33%) or 3 (n=11, 20%), while the control group showed a different distribution, with the majority having a score of 3 (n=19, 25%) or 1 (n=11, 14%). The CCI attributes include reliability, sensitivity, concurrent and predictive validity. In all study patients, an indwelling urinary catheter was placed as part of the clinical routine. Events potentially interfering with S100B levels were recorded as hypotonia (mean blood pressure < 65mmHg) or hypoxia (SpO_2 <90%). Group differences in age, sex, renal insufficiency, diagnosis, and mortality were assessed (Table 1).

	Neurotrauma n=54	**Control** n=75	**T-test** p-value
Age mean (min-max)	66 years (18-95)	69 years (36-91)	**.007**
Male	n=27 (50%)	n=34 (45%)	.600
Surgery	n=27 (50%)	n=75 (100%)	**.001**
Mortality	n=6 (12%)	n=9 (11%)	.356
Renal insufficiency	n=7 (14%)	n=14 (18%)	.631
Diagnosis	**Mild TBI** n=11 (20%) **Moderate TBI** n=7 (13%) **Severe TBI** n=10 (19%) **Stroke** n=17 (32%) **Tumor** n=6 (11%) **Spinal Injury** n=3 (6%)	**Abdominal surgery** n=37 (49%) **Orthopedic surgery** n=18 (24%) **Vascular surgery** n=11 (15%) **Urology** n=4 (5%) **Gynecology** n=5 (7%)	
Charlson Comorbidity Index			
Median	3	6	**.009**

Sample Collection and Processing in Serum

Blood samples were collected daily at 6:00AM, with 4mL of blood drawn into serum separator tubes. Following centrifugation at 1,300xG for 10 minutes at 4°C, cellular components were discarded, and the serum was stored at –80°C until analysis using commercially available kits on an automated immune analyzer (LIAISON® Sangtec®100 by chemiluminescence immunoassay on the Liaison analyzer, DiaSorin, Dietzenbach, Germany). S100B concentrations were determined using the standard curve generated from the absorbance of the standards, the sensitivity for the assay was 0.02ng/mL. We utilized for $S100B_{serum}$ cut-off values established in the 'Scandinavian Computed Tomography Guidelines' [27]. These guidelines incorporate $S100B_{serum}$ into diagnostics and recommend refraining from performing a computed tomography scan for $S100B_{serum}$ concentrations below 0.10µg/L [28]. The percentage of patients above the $S100B_{serum}$ cut-off levels is reported in the descriptive analyses.

Sample collection and processing in urine

Urine samples were collected systematically (daily at 6:00 AM) from all subjects during their stay on the intensive care unit, with each sample comprising 5–10 mL stored at –80°C until assay. Demonstrating the potential for a more accessible diagnostic method, prior research has highlighted the utility and accuracy of $S100B_{urine}$ levels in diagnosing brain damage in both pediatric [5] and adult populations [7]. Using the LIAISON® system, Schültke et al. reported normal adult $S100B_{urine}$ values for males (0.035±0.019µg/l) and females (0.042±0.017µg/l) [9]. Mean admission values following TBI were 0.04±0.019µg/l for mild, 0.055±0.021µg/l for moderate, and 0.038±0.006µg/l for severe TBI. Rodríguez-Rodríguez et al. established a cut-off value of 0.025 µg/l, which was deemed to offer heightened precision. This established cut-off value was methodologically integrated into our analysis [7].

Renal S100B Elimination

In order to exclude that an impaired kidney function interfered with the renal S100B elimination [19], we normalized for the creatinine clearance. Creatinine was analyzed with an enzymatic method, run on the Advia 2400 Chemistry system (Siemens Diagnostics, Tarrytown, NY, USA) based on the conversion of creatinine by creatinine deiminase. The reaction was monitored at 340nm, and the inverse rate was proportional to the creatinine concentration. According to the manufacturer, the overall coefficient of variability was 10.3%. Enzymatic assays of creatinine are generally more specific and sensitive than the conventional Jaffe alkaline picrate method.

The renal clearance K of a substance x is given by equation 1.

$$K_x = \frac{c_{x(Urine)} * Q_{Urine}}{c_{x(Serum)}} \quad (1)$$

Where c_x is the concentration of a substance x (in urine and in serum), and Q is the urine flow.

In order to adjust the S100B clearance for the renal function, i.e. to calculate the fractional excretion of S100B FE_{S100B}, the S100B clearance K_{S100B} was divided by the creatinine clearance $K_{creatinine}$ (see equation 2).

$$K_{S100B(adjusted)} = \frac{c_{S100B(Urine)} * c_{creatinine(Serum)}}{c_{S100B(Serum)} * c_{creatinine(Urine)}} \quad (2)$$

The reciprocal of the FE_{S100B} reflects the S100B reabsorption ratio.

Statistical Analysis

The statistical analysis was performed using SPSS 26 (SPSS Inc., Chicago, IL). Differences in the central tendency are tested for significance by applying Mann–Whitney-U tests, Wilcoxon tests, and non-parametric correlation. Besides, multiple linear regression was used to determine how well the Charlson Score can predict urine and serum levels while controlling for group, age, and sex. All values are given as mean ± standard error of mean (SE). Significance level was set to $p<0.05$.

Results

Comparing demographics, neurotrauma patients were significantly younger than controls (mean 66 vs. 69 years, p=.007) and suffered from less comorbidities (Charlson index 3 vs. 6, p=.009). All patients in the control group underwent surgery, half of the neurotrauma patients were operated. Pre-existing renal insufficiency and mortality were comparable (Table 1).

Following neurotrauma, $S100B_{serum}$ levels increased significantly after neurotrauma and in control patients, normalizing in the later ones on day 3 (Table 2). Comparing the control group to the neurotrauma group, the Mann-Whitney-Test shows significantly higher $S100B_{serum}$ level on day 3 (U=109.5, z=-2.198, p=.028) and day 4 (U=46.5, z=-2.213, p=.027) following neurotrauma. However, there was no significant difference at day 1 (U=1916.0, z=-.346, p=.729) and day 2 (U=345.5, z=-1.712, p=.087) (Table 2, Figure 1).

	Neurotrauma n=54		**Control n=75**		**T-test**
	Mean ± SE	Above cut-off	Mean ± SE	Above cut-off	p-value
S100B in serum, cut-off > 0.1 µg/l					
day1	0.48±0.80 µg/	n=43 (80%)	0.33±0.37 µg/l	n=64 (85%)	0.729
day2	0.81±1.56 µg/l	n=25 (46%)	0.23±0.14 µg/l	n=27 (36%)	0.087
day3	0.94±1.84 µg/l	n=17 (32%)	0.18±0.14 µg/l	n=10 (13%)	**0.028**
day4	0.86±1.67 µg/l	n=13 (24%)	0.15±0.15 µg/l	n=6 (8%)	**0.027**
day5	0.78±1.44 µg/l	n=12 (22%)	0.12±0.04 µg/l	n=4 (5%)	0.047
S100B in urine, cut-off > 0.025 ug/l					
day1	0.021±0.030 µg/l	n=19 (35%)	0.074±0.304 µg/l	n=36 (48%)	0.062
day2	0.033±0.059 µg/l	n=10 (19%)	0.055±0.109 µg/l	n=14 (19%)	0.37
day3	0.056±0.122 µg/l	n=8 (15%)	0.068±0.074 µg/l	n=12 (16%)	0.054
day4	0.040±0.069 µg/l	n=5 (9%)	0.049±0.061 µg/l	n=6 (8%)	0.221
day5	0.111±0.235 µg/l	n=6 (11%)	0.040±0.045 µg/l	n=4 (5%)	0.941
S100B fractional excretion					
day1	0.321 ± 1.023		1.316 ± 8.659		0.576
day2	0.168 ± 0.322		1.013 ± 2.489		0.446
day3	0.179 ± 0.268		1.665 ± 2.690		**0.001**
day4	0.310 ± 0.610		0.941 ± 1.375		**0.045**
day5	0.928 ± 2.694		1.508 ± 1.998		0.64

Table 2: Comparative analysis of S100B levels in serum, urine, and fractional excretion between neurotrauma patients (n=54) and control subjects (n=75) over five days. Mean values ± SE and the proportion of cases exceeding established cut-off values are presented for each day.

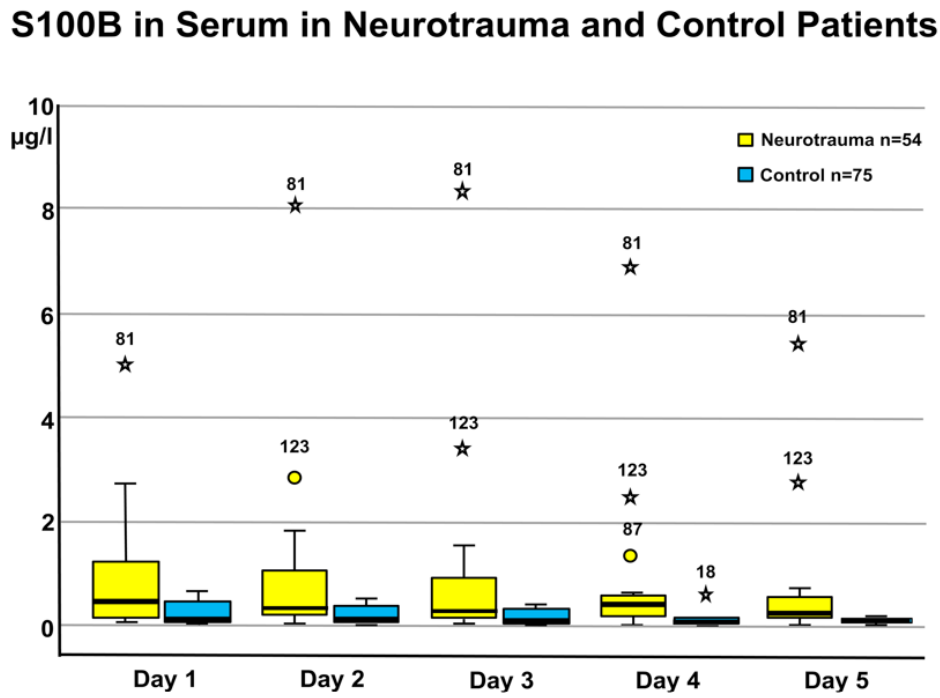

Figure 1: Temporal profile of S100B serum levels represented by comparative boxplot analysis between neurotrauma and control patients.

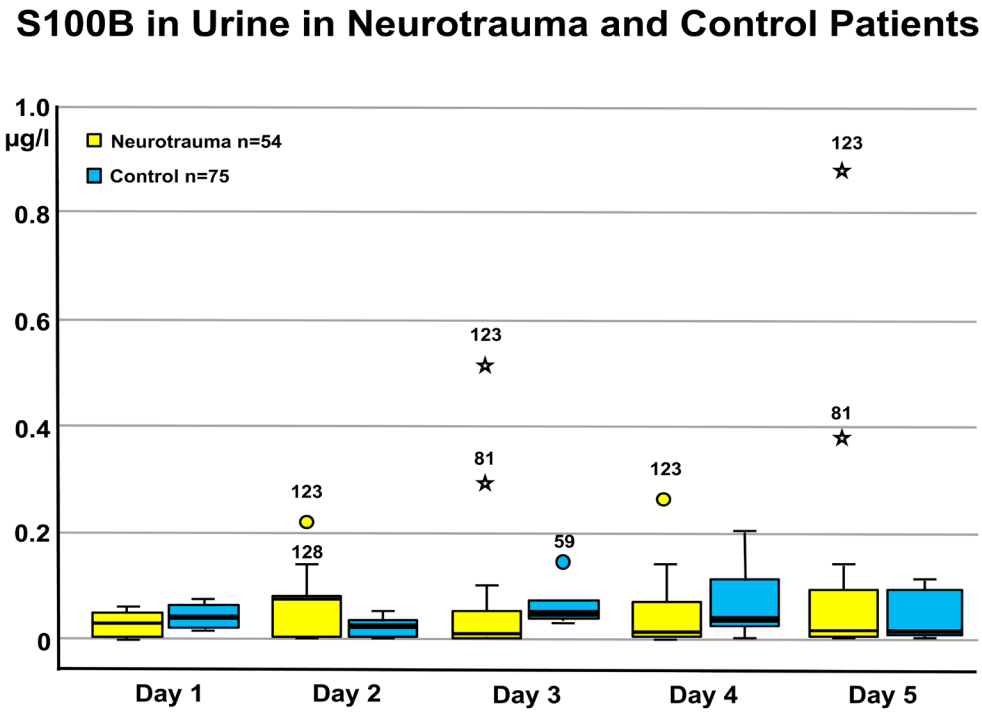

Figure 2: Temporal profile of S100B urine levels represented by comparative boxplot analysis between neurotrauma and control patients.

$S100B_{urine}$ levels were increased both in neurotrauma and control patients. Hence, no significant differences of $S100B_{urine}$ could be found (day 1: U=1657.0, z=-1.866, p=.062; day 2: U=408.0, z=-.897, p=.370; day3: U=113.0, z=-1.924, p=.054, day 4: U=61.5, z=-1.223, p=.221). To provide a comprehensive understanding of renal S100B elimination or reabsorption, we employed the ratio ($S100B_{urine}$/ $S100B_{serum}$) adjusted for creatinine clearance, as depicted in Figure 3. The fractional S100B excretion FE_{S100B} was significantly attenuated on day 3 day 3 (U=55.5, z=-3.274, p=.001) and 4 (U=45.0, z=-2.009, p=.045) following neurotrauma (Table 2). These differences remain significant even when controlling for age, sex, and Charlson Comorbidity Index (CCI).

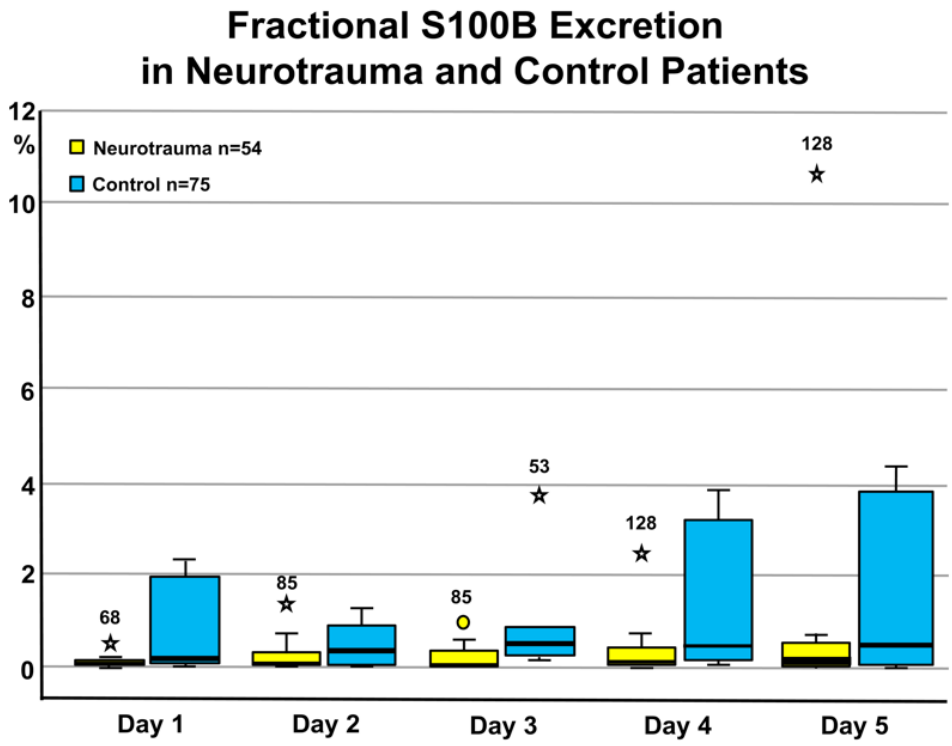

Figure 3: Temporal profile of S100B fractional excretion represented by comparative boxplot analysis between neurotrauma and control patients.

The Spearman correlation analysis demonstrates a significant relation (r_s=.306, p=.021) between $Creatinine_{serum}$ (day 1) and $FE_{Creatinine}$ (day 2) in both groups (control and neurotrauma group). However, splitting the sample in patients with renal insufficiency and patients without renal insufficiency demonstrates a non-significant tendency that this relation might only exist in patients with renal insufficiency (r=.800, p=.104, n=5), but not in patients without renal insufficiency (r=.090, p=.669, n=25). The small subsample size does not allow a definite statement.

Discussion

To the best of our knowledge, this is the first study to investigate concurrent concentrations of S100B in serum and urine in more than 120 patients longitudinally treated on an interdisciplinary intensive care unit. We demonstrated the 21 KD neurotrophic protein S100B not to be completely reabsorbed in the kidneys, and urine measurements may thus offer an alternative source to screen for elevated S100B levels. Furthermore, we found an attenuated renal S100B elimination following CNS injury suggesting a physiological conservation system for neurotrophic proteins. The injury-induced S100B release in neuronal-glial cultures displayed an upward slope over the investigation period [14] demonstrating an active stimulated release following experimental injury contributing to the total S100B concentration measured. However, since a strong S100B immunopositivity of the ependymal and choroid plexus epithelia was observed although the functional consequences were not elucidated yet, we cannot exclude any contribution from these cells to the CSF concentration [29]. However, knowledge about the release and wash-out pattern of S100B in CSF and serum is as crucial [30] as the subsequent renal elimination. Since literature review identified a paucity of studies investigating S100B in urine or its elimination kinetics in

adults, we designed the present longitudinal study. In accordance with Jönsson et al. [30] we did not find any correlation of renal function with either $S100B_{urine}$ or FE_{S100B}. However, we did not include patients with renal failure suggested to increase S100B serum levels [24]. Nevertheless, to control the experimental groups for renal function, we verified that the percentage of patients with renal insufficiency was comparable. While Schültke et al. reported gender specific different normal $S100B_{urine}$ values in adults [9], we opted to use the slightly lower gender-nonspecific normal $S100B_{urine}$ values of Rodríguez-Rodríguez et al. at 0.025 µg/l [7]. In order to avoid any gender effects, we controlled the experimental groups for gender.

The notion that S100B in urine is biased by extracranial trauma [6]is confirmed by our study demonstrating almost higher $S100B_{urine}$ levels following elective extracranial surgery (Figure 2). Studies report the relevance of S100B in urine as a valuable outcome predictor in infants [25] and adults [33] applying a group comparison survival vs. death. Since we controlled our experimental groups for mortality, we failed to confirm this notion. However, our control group comprising of patients undergoing elective extracranial surgery demonstrated not just elevated $S100B_{urine}$ levels, but also in a substantial percentage of patients $S100B_{serum}$ was above the cut-off-levels implemented in Scandinavia for decision making to initiate a computed tomography [28]. Whether the increased $S100B_{serum}$ levels in control patients admitted to the intensive care unit because of elective major extra cranial surgery result from tissue hypo perfusion [32] or surgical or anesthetic procedures often attributed to postoperative cognitive decline [33] has to be elucidated in future studies. Remarkably, individuals suffering from CNS injury exhibiting elevated $S100B_{serum}$ levels demonstrated a significantly reduced renal elimination of S100B, indicative of a net reabsorption. Consistent with this finding, Schultke et al. reported a serum/urine ratio of S100B at 2:1 in healthy subjects, escalating to 15:1 in severe TBI patients. Their study revealed a non-linear relationship between S100B serum and urine levels, emphasizing that urinary excretion did not increase proportionally with rising serum concentrations [9]. On the other hand, in an animal model of hepatic encephalopathy, urinary S100B excretion increased simultaneously with $S100B_{serum}$ levels [19]. The different handling of the neurotrophic protein following CNS injury where S100B is required for regenerative properties versus hepatic encephalopathy where increased $S100B_{serum}$ levels are a side product of organ failure indicate that biomarker represent a physiological rescue system rather than a labelling system for physicians [34].

Conclusion

The 21kD neurotrophic protein S100B is not completely reabsorbed in the kidneys following an increased release into serum, and urine measurements may thus offer an alternative source to screen for elevated S100B levels. Major surgery even without concomitant brain injury does affect S100B serum and urine levels significantly. Although there is a reasonable desire for a reliable indicator to accurately determine the extent of brain injury and to monitor therapeutic interventions, advocating S100B in this role remains problematic. While a substantial body of evidence demonstrates an association between S100B and bad outcome after brain injury, it is important to be aware that proof of an association is not proof of causation in science. In the present prospective longitudinal study, the concurrent measurement of S100B in serum and urine, we found opposite to common reasoning, the renal elimination of S100B attenuated following acute CNS injury thereby suggesting a physiological conservation system for neurotrophic proteins. It is important to note that similar pitfalls may apply to other biomarker as long as the physiological function of the respective protein is not considered.

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