



# Serum Neuron Specific Enolase and S-100B Levels in Hemodialysis and Peritoneal Dialysis Patients

Medine Alpdemir<sup>1</sup>, Oğuzhan Özcan<sup>2</sup>, Mehmet Fatih Alpdemir<sup>1</sup>, Mehmet Şeneş<sup>3</sup>, Alper Azak<sup>4</sup>, Murat Duranay<sup>5</sup>, Doğan Yücel<sup>3</sup>

<sup>1</sup>Balıkesir State Hospital, Biochemistry, Balıkesir, Turkey

<sup>2</sup>Hatay Mustafa Kemal University Faculty of Medicine, Department of Medical Biochemistry, Hatay, Turkey

<sup>3</sup>Ankara Training and Research Hospital, Department of Biochemistry, Ankara, Turkey

<sup>4</sup>Balıkesir State Hospital, Nephrology, Balıkesir, Turkey

<sup>5</sup>Ankara Training and Research Hospital, Department of Nephrology, Ankara, Turkey

## Abstract

**Objective:** Neuron-specific enolase (NSE) and S-100B are brain-derived proteins, and their levels increase in brain injury. The aim of the study was to determine serum S-100B and NSE levels in patients with end-stage renal disease undergoing hemodialysis (HD) and peritoneal dialysis (PD) and to demonstrate how these levels were affected by the type of dialysis applied.

**Methods:** The study group consisted of age- and gender-matched 20 patients undergoing HD, 26 patients undergoing continuous ambulatory PD (CAPD) and 21 healthy controls. Blood samples were obtained before and after dialysis in the HD patient group, and fasting blood samples were obtained in the CAPD and control groups. The routine biochemical parameters were measured within two hours from all serum samples. The remaining serum samples were stored at -80 °C until the day of analysis of the S-100B and NSE assays. Serum S-100B and NSE levels were measured by chemiluminescence immunoassay method. Routine biochemistry tests were measured by colorimetric method using a biochemistry analyzer.

**Results:** Serum S-100B (0.11±0.06 ng/mL in HD, 0.13±0.09 ng/mL in CAPD and 0.05±0.03 ng/mL in controls) and NSE (12.7±5.99 ng/mL in HD, 9.26±5.52 ng/mL in CAPD and 6.82±2.36 ng/mL in controls) levels were higher in HD and CAPD groups compared to controls. S-100B and NSE levels were higher after HD compared to before HD (p<0.001). There was a weak but significant correlation between S-100B and NSE levels (r=0.290; p=0.006).

**Conclusion:** In this study, serum S-100B and NSE levels were found to be high in patients undergoing HD and PD. Serum S-100B and NSE concentrations were higher in HD and CAPD patients. Increased S-100B and NSE levels may be associated with cerebrovascular events in patients with chronic renal failure. They may also be important markers for the determination of cerebrovascular events.

**Keywords:** Brain damage, end stage renal failure, hemodialysis, neuron-specific enolase, peritoneal dialysis, S-100B

## INTRODUCTION

Neuron-specific enolase (NSE) and S-100B are specific brain-derived proteins that have recently gained importance as neurochemical markers (1). Serum concentrations of these analytes increase after traumatic brain injury and clinical conditions that result in brain injury, such as cardiac arrest and cardiopulmonary bypass surgery (2, 3). S-100B is a calcium-

binding protein, approximately 21 kDa in weight and composed of subunits A and B. Subunit B is synthesized mainly by astroglial and microglial cells and is highly specific for the central neurological system (4, 5). The half-life of S-100B in the serum is reported to be approximately two hours, and it is metabolized and excreted by the kidneys. Its concentrations are normally undetectable in serum samples, but can reach measurable levels



**Address for Correspondence:** Medine Alpdemir, Balıkesir State Hospital, Biochemistry, Balıkesir, Turkey  
**E-posta:** bitigic@hotmail.com **ORCID ID:** orcid.org/0000-0003-2625-0246

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following certain clinical conditions such as stroke, subarachnoid hemorrhage, head trauma, and extracorporeal circulation (6-8).

NSE is a dimeric isoenzyme of the glycolytic enzyme enolase that is approximately 78 kDa in weight and has a biological half-life of about 24 hours. It is highly localized in neurons and neuroendocrine cells, and constitutes 1.5% of soluble proteins in brain tissue (9). When brain tissues are injured, NSE diffuses into cerebrospinal fluid (CSF) and systemic circulation (1, 10). Recent studies have suggested that increased NSE concentrations in serum and CSF can be used as a sensitive and quantitative marker for parenchymal damage in brain tissue, cerebral infarction and intracerebral hemorrhage (9, 11).

Chronic renal disease is defined as an irreversible and progressive decrease ( $<60$  mL/min/1.73 m<sup>2</sup>) in the glomerular filtration rate (GFR). When chronic and progressive deterioration reaches an advanced stage, it is called chronic renal failure (CRF). CRF is associated with severe disorders in the fluid and electrolytes balance, as well as in metabolic-endocrine functions. It is well known that decreased GFR is a risk factor for cerebrovascular and cardiovascular diseases. Cerebrovascular diseases are considered as one of the most important causes of higher morbidity and mortality in patients with end-stage renal disease (ESRD). It has been reported that there is a relationship between ESRD and several cerebral pathologies, including stroke, cerebral microvascular disease, silent lacunar infarct, white matter lesions and cerebral microvascular hemorrhages (12).

Controlling these risk factors plays a key role in the prevention of cerebral diseases and improving the quality of life of patients with ESRD. Magnetic resonance imaging (MRI) is still the most valuable diagnostic tool and is commonly used in the diagnosis of cerebrovascular diseases in these patients. As neurochemical markers, serum S-100B and NSE can be useful for early diagnosis of brain damage.

The purpose of this study was to determine serum NSE and S-100B levels in patients undergoing hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD), to compare these values with the control group, and to assess these neurochemical markers before and after a single HD session.

## METHODS

### Subjects

Twenty patients who underwent HD and 26 patients who underwent CAPD were included in the study. Twenty-one age- and gender-matched healthy controls without any systemic disease such as hypertension, chronic renal disease,

diabetes mellitus, cardiovascular or neurovascular disease were selected for the study. The study was approved by the Ethics Committee of Ankara Hospital (Approval no: 3020) in accordance with the regulations of the Ministry of Health. All patients were informed about the study procedures before being included.

### Blood Sampling and Biochemical Analysis

Fasting venous blood samples were obtained from the patients before and after a HD session, while only fasting blood samples were obtained from the CAPD group and controls. Blood samples were drawn into evacuated serum separator tubes containing clot activator (SST Vacutainer®, Becton Dickinson). All blood samples were centrifuged at 1500 g for 10 minutes. Sera were separated and used for routine biochemical testing within two hours. The remaining serum samples were stored at -80 °C until the day of analysis for S-100B and NSE assays.

Serum glucose, urea, creatinine (Cre), uric acid (UA), total protein (TP), albumin (Alb), sodium (Na) and potassium (K) levels were measured with original reagent using Olympus AU 2700 analyzer (Mihsima Olympus Co. Ltd. JAPAN).

### S-100B and NSE Procedure

Serum S-100B and NSE measurements were conducted using immunochemistry (Liaison® Sangtec 100, DiaSorin AB Bromma, Sweden). The minimal detection concentration was 0.02 ng/mL for S-100B and 0.04 ng/mL for NSE. The intra-assay coefficient of variation (CV) was 3.7% for S-100B and 0.9% for NSE. The inter-assay CVs for S100-B and NSE were 5.7% and 5.3%, respectively.

### Dialysis Procedure

All patients underwent HD three times a week for four hours per day, using a synthetic low-flux hollow-fiber filter (polysulfone membrane) (surface area 1.25 m<sup>2</sup>), with an average blood flow rate of 200-300 mL/min, and a dialysate flow rate of approximately 500 mL/min during the HD procedure. For peritoneal dialysis patients, CAPD involved four or five dwells per day of 2-2.5 liters per dwell.

### Statistical Analysis

Descriptive statistics were used to analyze the data. Kolmogorov-Smirnov test was used for normality testing of the data. Differences between groups were analyzed using the Mann-Whitney U test. Spearman correlation was used to evaluate the association between variables. Pre- and post-HD values were compared using the Wilcoxon sign test.  $P < 0.05$  was considered statistically significant. Statistical analyses were conducted using SPSS version 15.0.

## RESULTS

Demographic data and biochemical test results are given in Table 1 and Table 2, respectively. Serum S-100B and NSE levels

Table 1. Demographic data of control and patient groups			
Variables	Control (n=21)	CAPD (n=26)	HD (n=20)
Gender			
Female (%)	9 (43%)	12 (46%)	9 (45%)
Male (%)	12 (57%)	14 (54%)	11 (55%)
Age, year (mean ± SD)	47.9±8.5	46.8±13.3	49.37±15.17
Body mass index, kg/m <sup>2</sup> (mean ± SD)	27.7±3.7	25.35±5.2	22.58±3.2
Dialysis duration, years			
<1	-	4	5
1-5	-	17	10
5-10	-	5	5
Smoking (%)	4 (19%)	6 (23%)	2 (10%)
Diabetes mellitus (%)	-	6 (23%)	5 (25%)
Bone disease (%)	-	3 (12%)	4 (20%)
Cardiovascular disease (%)	-	2 (8%)	1 (5%)
Hypertension (%)	2	12 (46%)	14 (70%)
Dyslipidemia (%)	3	3 (12%)	8 (40%)
Thyroid disease (%)	2	3 (12%)	-
Family history (%)	-	1 (4%)	3 (15%)
Drugs used (%)			
Antilipidemic drugs	-	3 (12%)	8 (40%)
Antihypertensive drugs	-	21(81%)	14 (70%)
-Beta blockers	-	3 (12%)	2 (10%)
-ACE inhibitors	-	4 (19%)	6 (30%)
-Angiotensin II receptor blockers	-	5 (13%)	2 (10%)
-Calcium channel blockers	-	9 (35%)	6 (30%)
-Adrenergic receptor blockers	-	4 (13%)	-
Insulin	-	6 (23%)	5 (25%)
Folic acids and derivatives	-	13(50%)	20 (100%)
Drugs containing iron	-	10 (38%)	20 (100%)
Phosphate chelators	-	24 (92%)	20 (100%)
Vitamin D analogues	-	24 (92%)	20 (100%)
Erythropoietin analogues	-	5 (9%)	20 (100%)
Antiaggregant drugs	-	1 (4%)	-
Aspirin	-	2 (8%)	-
Tricyclic antidepressants	-	2 (8%)	-
T3 agonists	-	2(8%)	-

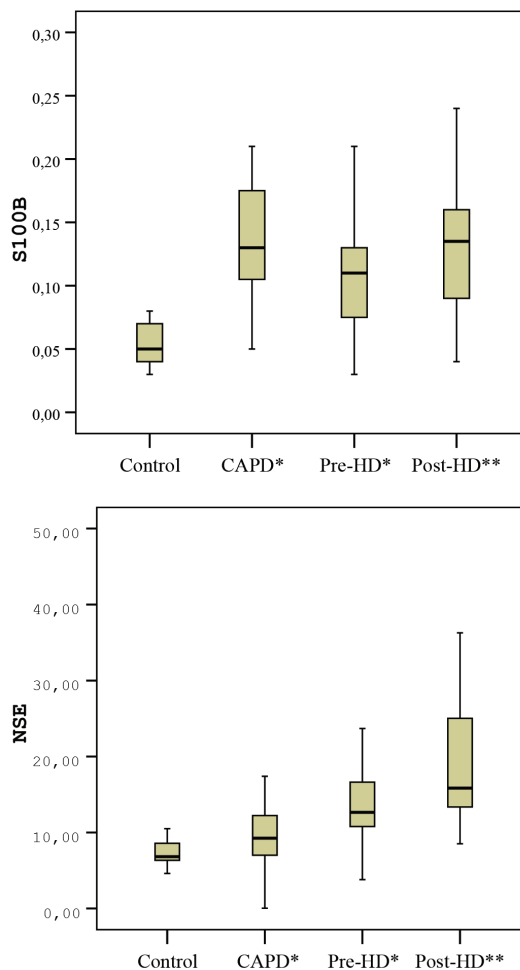
CAPD: Continuous ambulatory peritoneal dialysis, HD: Hemodialysis, SD: Standard deviation

are given in Table 3. Serum S-100B and NSE levels were higher in HD group than in the control group (p=0.001, p=0.002, respectively). Serum S-100B and NSE levels were higher in CAPD group than in the control group (p=0.002, p=0.009, respectively). Serum S-100B and NSE levels were significantly different between CAPD and HD groups (p=0.023, p<0.001, respectively) (Table 3). There was a significant positive correlation between S-100B and NSE levels (r=0.290; p=0.006). S-100B and NSE levels were also significantly higher following a single HD session (p<0.001) (Table 4). S-100B and NSE results are shown in Figure 1.

## DISCUSSION

The dialysis process may affect several biochemical factors. While many of these changes are beneficial, others can be harmful and increase the severity of the disease.

In the current study, both S-100B and NSE levels were found to be increased in patients undergoing HD and CAPD. When we evaluated the difference between the dialysis types, we found



**Figure 1.** Serum S-100B and NSE levels in the patient and control groups  
CAPD: Continuous ambulatory peritoneal dialysis, HD: Hemodialysis

that serum S-100B levels were higher and NSE levels were lower in the CAPD group than in the HD group. The kidneys normally metabolize both S-100B and NSE; therefore, in renal failure, serum levels may be expected to be higher due to decreased renal clearance. Considering the relationship between chronic renal disease and cerebrovascular disorders in these patients, increasing levels of serum S-100B and NSE may be associated with neurological tissue injury.

In this study, we also evaluated the HD effect and found that both serum S-100B and NSE levels were higher in post-HD compared to pre-HD. This could be the result of the hemodilution effect that occurs normally prior to HD and partial hemoconcentration due to dialysis therapy. Another factor contributing to higher levels following HD could be the insufficient permeability of the synthetic hollow-fiber membrane to the S-100B and NSE proteins that could result in ineffective removal. However, there is no study investigating the effect of dialysis on serum S-100B and NSE levels in the literature..

Cerebrovascular diseases are one of the most common reasons for high morbidity and mortality in patients with ESRD (1, 13). The early diagnosis of cerebrovascular disease is important to improve the prognosis and quality of life of these patients. In a previous study, Ikram et al., (14) observed that there was a relationship between decreased GFR levels and the findings in MRI, including cerebral microvascular lesions. Several other studies have reported that decreased GFR is related to an increased prevalence of subclinical lacunar cerebral infarcts detected using MRI (15, 16). In another study, decreased GFR was found to be associated with silent cerebral infarcts (17). Kim et al., (18) investigated the association between depression symptoms and serum S-100B concentrations and found that S-100B levels increased in ESRD due to glial pathology and dysfunction of the blood brain barrier. According to these previous studies, we can say that varying degrees of reduction in GFR levels are associated with cerebral pathologies in patients with chronic renal disease. In the diagnosis of cerebrovascular diseases, the measurement of serum S-100B and NSE provides significant advantage since it

**Table 2. The measured biochemical parameter levels in the control and patient groups**

Parameters (measuring units)	Control (n=21) M (IQR)	CAPD (n=26) M (IQR)	p*	HD (n=20) M (IQR)	p*
Glucose (mmol/L)	5.2 (1.6)	7.2 (4.7)	<0.001	6.9 (6.7)	<0.001
Urea (mmol/L)	10.6 (3.2)	40.2 (12.4)	<0.001	46.7 (10.2)	<0.001
Creatinine (µmol/L)	88 (18)	778 (239)	<0.001	787 (265)	<0.001
Uric Acid (mmol/L)	0.29 (0.06)	0.34 (0.07)	0.042	0.33 (0.06)	0.042
Total protein (g/L)	69 (5)	67 (9)	0.062	68 (6)	0.070
Albumin (g/L)	42 (4)	37 (4)	0.001	36 (4)	0.001
Na (mmol/L)	139.3 (2.5)	138.6 (3.4)	0.125	136.0 (5.0)	0.102
K (mmol/L)	4.4 (0.4)	4.3 (0.5)	0.086	5.4 (0.8)	0.001
Systolic blood pressure (mmHg)	115 (12)	132 (19)	0.001	142 (19)	0.001
Diastolic blood pressure (mmHg)	75 ( 6)	82 (9)	0.001	80 ( 11)	0.001

\*p value; comparing control and study groups. CAPD: Continuous ambulatory peritoneal dialysis, HD: Hemodialysis, M: Median, IQR: Inter quartile range

**Table 3. Comparison of serum S-100B and NSE levels in the control and patient groups**

Parameters (measuring units)	Control (n=21) M (IQR)	CAPD (n=26) M (IQR)	p*	HD (n=20) M (IQR)	p*	p**
S-100B (ng/mL)	0.05 (0.03)	0.13 (0.09)	0.002	0.11 (0.06)	0.001	0.023
NSE (ng/mL)	6.82 (2.36)	9.26 (5.52)	0.009	12.7 (5.99)	0.002	<0.001

\*p value; comparing control and study groups. \*\*p value; comparing CAPD and HD. CAPD: Continuous ambulatory peritoneal dialysis, HD: Hemodialysis, M: Median, IQR: Inter quartile range

**Table 4. Comparison of serum S-100B and NSE levels before and after hemodialysis**

Parameters (measuring units)	Before (n=20) M (IQR)	After (n=20) M (IQR)	p*
S-100B (ng/mL)	0.11 (0.06)	0.13 (0.07)	<0.001
NSE (ng/mL)	12.7 (5.99)	15.84 (11.72)	<0.001

\*p value; comparing before and after hemodialysis, M: Median, IQR: Inter quartile range

is easy to perform and non-invasive; however, there is no study in literature investigating S-100B and NSE concentrations in patients with ESRD, and the present study is the first in this field.

## CONCLUSION

In this study, we determined that serum S-100B and NSE levels increased in patients undergoing HD and CAPD therapy compared to controls. Therefore, these markers might be valuable in determining the possible risk of a cerebrovascular event in patients with chronic renal disease. Nevertheless, one of the limitations of this study was that further studies are needed to compare serum S-100B and NSE levels with MRI findings in patients with CRF. Another limitation was that study cohort was relatively small.

### Ethics

**Ethics Committee Approval:** The study was approved by the Ethics Committee of Ankara Hospital (approval no: 3020) in accordance with the regulations of the Ministry of Health.

**Informed Consent:** All patients were informed about the study procedures before being included.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.Ş., A.A., M.D., D.Y., Concept: M.A., O.Ö., M.Ş., D.Y., Design: M.A., O.Ö., M.Ş., Data Collection or Processing: M.A., O.Ö., M.F.A., M.Ş., Analysis or Interpretation: M.A., D.Y., Literature Search: M.A., O.Ö., M.F.A., Writing: M.A., O.Ö., D.Y.

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