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# The Impact of Inflammation and Autonomic Nervous System Activity on Cognitive Impairment during a Hemodialysis Session

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## Abstract

**Background:** Cognitive dysfunction is a common abnormality found in Chronic Kidney Disease (CKD) patients and especially during hemodialysis (HD) treatment. It is supported that inflammation and Autonomic Nervous System (ANS) dysfunction are implicated in cognitive impairment. The aim of this study was to determine the relationship between inflammation, ANS activity and cognitive function during a HD session.

**Methods:** 15 HD patients gave informed consent to participate in this study. Autonomic Nervous System activity was evaluated by the method of pupillometry, cognitive function with the Mini Mental State Examination (MMSE) questionnaire, and inflammation with the biomarker of C-Reactive Protein (CRP) before and after a dialysis session.

**Results:** After the HD session, from the pupillometric indices only Average Dilation Velocity decreased by 5.2% ($p<0.05$) and MMSE score decreased by 14.3% ($p<0.05$). After the HD session CRP levels significantly increased by 39.6% ($p<0.05$). Before HD therapy MMSE score was significantly correlated with years in HD therapy ($r=-0.663$, $p=0.014$), Maximum Constriction Velocity ($r=-0.744$, $p=0.001$) and CRP levels ($r=-0.621$, $p=0.013$). Similarly, after the completion of the HD therapy MMSE was correlated with years in HD therapy ($r=-0.767$, $p=0.002$), Maximum Constriction Velocity ($r=-0.597$, $p=0.019$) and CRP levels ($r=-0.513$, $p=0.05$).

**Conclusion:** The results of the present study suggest that inflammation and ANS function, which are deteriorated after the dialysis session, seem to contribute to cognitive impairment in HD patients.

**Keywords:** Autonomic nervous system; Cognitive impairment; Hemodialysis treatment; Inflammation; Pupillometry

## Introduction

Patients with chronic kidney disease (CKD) experience many clinical complications due to morphological and functional changes in all systems and accordingly these complications affect their morbidity and mortality rates. Cognitive dysfunction and dementia is a common complication found in CKD patients, detectable even in the early stages [1]. Especially those patients in end-stage renal disease (ESRD) are at high risk of cognitive dysfunction development and dementia [2,3]. Indeed, it has been estimated that the prevalence of cognitive impairment in dialysis (HD) patients is around 30-60% [2,4]. Moreover, it has been found that GFR is associated with cognitive decline in CKD patients and accordingly as GFR reduces patients experience cognitive deficits [2,5]. In a study by Murray et al. patients with GFR<30 ml/min 1.73 $m^2$ had significantly worse results in memory tests, processing speed, and executive function compared to those with GFR ≥ 30ml/min 1.73 $m^2$ [6].

Reaction time, mental speed, verbal memory, focused concentration, visual scanning and choice reaction time are components of cognitive function, which in CKD patients are usually progressively reduced [7]. Neuroimaging studies suggested that cerebral damage due to ischemia [8], cerebral atrophy [9], brain degeneration of toxic-metabolic aetiology [3] and progressive intracranial deep white matter lesions [10] are the main causes of impaired cognitive function in these patients. Moreover, anaemia and reduced haemoglobin concentration have been associated with cognitive impairment, which improves after treatment with erythropoietin [11]. Furthermore, presence of chronic inflammation may have a role in the

aetiology of mild cognitive impairment [12]. Specifically, a relation between the levels of C-reactive protein (CRP) and interleukin-6 (IL-6) with reduced cognitive performance in healthy subjects and in older adults has been suggested [13]. In addition, in HD patients it has also been found that abnormal production of cytokines is associated with cognitive impairment [14].

Besides inflammation, there is evidence that ANS dysfunction is associated with mild cognitive function [15]. In patients with Alzheimer's disease (AD) and Myasthenia Gravis the strong relationship between acetylcholine mediated neurotransmission and cognitive function has led to the development of the cholinergic hypothesis [16,17]. According to this, the degeneration of cholinergic neurons in the basal forebrain and the associated loss of cholinergic neurotransmission in the cerebral cortex and in other areas, contributed significantly to the deterioration in cognitive function observed in patients with AD [18,19] and Myasthenia Gravis [20].

Dialysis treatment increases the inflammation due to possible vascular access infections, bio-incompatible dialysis membrane, dialysate, endotoxin exposure, back filtration and chronic infections [21]. Moreover, ANS dysfunction is a well-known complication that characterizes CKD patients and especially those on HD treatment [22]. However, there is no study to correlate and examine the effects of inflammation and ANS dysfunction in ESRD patients in the literature. Thus, the aim of this study was to determine the relationship between inflammation, ANS activity and cognitive function during a HD session.

# Methods

## Patients

From the 98 patients who undergo HD in the Renal Unit of AHEPA University Hospital in Thessaloniki, Greece, 21 volunteered to participate in the study. Among them, 15 HD patients were eligible to participate in the study. All participants were free of any ophthalmological disorder and had symmetrical pupils. The entry criteria were: being on HD therapy for 4 hours, 3 times/week for at least six month. Patients were excluded from the study if they had any of the following criteria: unstable hypertension, congestive heart failure (grade>II according to NYHA), cardiac arrhythmias, anaemia (Hb<10 g/dL), recent myocardial infarction, unstable angina, diabetes mellitus, active liver disease or previous established cause of syncope. No patient had underlying vascular disease and no patient with renal failure due to Alport syndrome, who may have also had ocular manifestation, participated in the study. Moreover, patients with medications that may affect the cardiovascular or ANS system or pupillary light reflex were excluded from the study.

All patients had a forearm arteriovenous fistula as a vascular access to receive the HD treatment and they underwent HD therapy (NIKKISO: Dialysis system DBB-05, Germany) using low flux, hollow fibre dialyzers and bicarbonate buffer. An enoxaparin dose of 40-60 mg was administered intravenously before the beginning of each HD session while EPO therapy was given after the completion of HD session in order to normalize haemoglobin levels within 11-12 (g/dL).

The purpose, nature, method and potential risks of the study were explained to all participants. The study was approved by the Human Research and Ethics Committee of the AHEPA University Hospital and the Aristotle University of Thessaloniki Ethics Committee. All patients gave written informed consent prior to the study participation.

## Study design

All measurements took place 30 min before the onset of the HD therapy and 30 min after the HD therapy. Subjects were studied in a quiet, comfortable room with controlled temperature between 25° and 28° degrees Celsius. At first, patients completed the Mini-Mental State Examination (MMSE) questionnaire. Thereafter, ANS function was assessed simultaneously using pupillometric and Heart Rate Variability (HRV) measurements. The participants were asked to avoid caffeine and alcoholic beverages a day before the measurements. Finally, blood samples were collected for C-reactive protein (CRP) analysis. All tests were conducted and interpreted by the same researcher.

# Measures

Before and immediately, namely 15 min after the completion of the dialysis session, all participants underwent the following evaluation:

## Cognitive function assessment

Mini-Mental State Examination (MMSE) [23] in Greek [24], which includes 11 items and requires 7-10 minutes to complete, was used for the cognitive function evaluation. MMSE is a self-administered questionnaire and evaluates orientation, attention, memory, concentration, language and constructional ability [25]. The total score ranges from 0 to 30 and reflects the number of correct responses [26]. A score from 30 to 24 indicates normal cognitive function while scores below 24 reflect cognitive impairment, which could be mild (score between 19-23), moderate (score between 10-18) or severe (score below or equal to 9).

## Pupillometry

The hand-held infrared pupillometer (NeurOptics PLR-200™ City and Country) was used to measure the pupil size and the pupillary light reflex [27]. The pupillometer uses infrared imaging technology and it requires no calibration by the user. Pupillometry was performed on each eye separately. Each eye was assessed three times with 5 minute intervals. The pupillometric indices were:

- maximum pupil size, namely the baseline pupil diameter after 2 min dark adaptation, which is an indicator of symaptho-vagal balance [28]


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- minimum pupil size, which is generally defined as a marker of sympatho-vagal balance, since it is involved in the second segment of the V-shaped pupillometric response [29]
- constriction, which is modulated by PNS activity [29]
- latency, which is an index of sympatho-vagal balance [29]
- average constriction velocity
- maximum constriction velocity, which are both sensitive indices of PNS activity [29]
- average dilation velocity, which reflects sympatho-vagal balance [29] and
- 75% pupil size recovery time, which is an index of SNS activity [29]. An average of the three measurements was recorded as the final value.

### Inflammation status

The blood samples were collected in tubes containing EDTA and were immediately centrifuged. Serum CRP was detected using the immunonephelometric assay, which uses particle-enhanced immunonephelometry, on the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc, Deerfield, IL) [30]. Before the analysis, a 20-fold dilution of each sample was performed automatically by the instrument. The assay was standardized against the CRM 470 reference.

### Statistical analysis

The mean scores and the standard deviations (SD) were calculated with descriptive statistics for all groups. Student's paired t-tests were performed to compare the data between the left and right eye. The analysis of two-way ANOVA with repeated measures was then employed for the comparison of the values obtained with MMSE, pupillometry and CRP before and after the HD, followed by Bonferroni adjustment to pinpoint differences. Correlations between values were analyzed with Pearson's correlation coefficient. Moreover, Multiple Regression analysis was conducted to examine the possible factors that influence cognitive function. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL), version 16.0, software for Windows (Microsoft Corp, Redmond, WA). A two-tailed $p<0.05$ was considered statistically significant.

## Results

The clinical data of the participants are shown in Table 1. Before the HD treatment 46.6% of the participants had mild cognitive impairment, while 20% had moderate cognitive impairment and 33.3% had normal cognitive cognition. After the HD treatment MMSE score was by14.3% ($p<0.05$) decreased. More precisely, only 6.6% of the participants had normal cognition. 46.6% of the participants had moderate cognitive impairment, 40% mild cognitive impairment and 6.6% showed severe cognitive impairment.

No significant differences between left and right eye were found. Therefore the results of the right eye are presented for the rest of analyses. The results of ANS function measured with pupillometry, inflammation evaluated with CRP index and cognitive function assessed with MMSE before and after the HD session are presented in Table 2. Following HD therapy, from the pupillometric indices, only Average Dilation Velocity was found to be by 5.2% ($p<0.05$) decreased. Moreover, CRP levels were increased by 39.6% ($p<0.05$) after the HD session.

**Table 1:** Clinical data of subjects (mean ± SD).

| | **Patients** |
|---|---|
| Subjects (n) | 15 |
| Male/Female | 7/8 |
| Age (Years) | 48.7 ± 14.8 |
| Height (cm) | 1.67 ± 0.11 |
| Weight (Kg) | 74.6 ± 14.4 |
| BMI | 26.6 ± 5.2 |
| Years on HD | 7.7 ± 4.53 |
| **Parameter**<br>Causes Of Chronic Kidney Disease | **N** |
| Polycystic kidney disease | 4 |
| Tumor | 1 |
| Glomerulonephritis | 4 |
| Vesicaureteral reflux | 1 |
| Urinary tract obstruction | 2 |
| Albort disease | 0 |
| Nefrosclerosis | 2 |
| SLE (Systemic lupus erythematosus) | 0 |
| Miscellaneous or unknown causes | 1 |
| **Medications** | |
| Beta receptor blocker | 7 |
| Calcium channel antagonistic | 14 |
| Digitalis | 4 |

Before and after HD therapy, the MMSE score was significantly correlated with years in HD therapy ($r=-0.663$, $p=0.014$ and $r=-0.767$, $p=0.002$, respectively) (Figures 1 and 2), Maximum Constriction Velocity ($r=-0.744$, $p=0.001$) (Figure 3) and CRP levels ($r=-0.621$, $p=0.013$) (Figure 4). After the completion of the HD therapy, MMSE was also correlated with years in HD therapy, Maximum Constriction Velocity ($r=-0.597$, $p=0.019$) (Figure 5) and CRP levels ($r=-0.513$, $p=0.05$) (Figure 6).

**Table 2:** Results of ANS function measured with pupillometry, inflammation evaluated with CRP index and cognitive function assessed with MMSE before and after the HD session.

| Parameters | Patients | | | | | |
|---|---|---|---|---|---|---|
| | Before HD | | | After HD | | |
| | Mean±SD | 95% Confidence Interval of the Difference | | Mean±SD | 95% Confidence Interval of the Difference | |
| | | Lower Bound | Upper bound | | Lower Bound | Upper bound |
| Hemodynamic Parameters | | | | | | |
| Systolic blood Pressure (mmHg) | 127.07±12.06 | 119.78 | 134.36 | 121.07±19.64 | 109.20 | 132.94 |
| Diastolic Blood Pressure (mmHg) | 78.23±17.53 | 67.63 | 88.82 | 69.38±13.46 | 61.24 | 77.52 |
| Heart rate (beat) | 73.00±5.62 | 69.59 | 76.40 | 79.53±10.94 | 72.92 | 86.15 |
| Pupillometric indices | | | | | | |
| Maximum pupil diameter (mm) | 4.37±0.90 | 3.82 | 4.92 | 4.29±1.13 | 3.57 | 5.01 |
| Minimum pupil diameter (mm) | 2.85±0.71 | 2.42 | 3.29 | 2.92±0.72 | 2.46 | 3.39 |
| Constriction (%) | -33.34±3.43 | 31.26 | 35.42 | -31.41±4.39 | 28.62 | 34.21 |
| Latency (sec) | 0.25±0.02 | 0.24 | 0.27 | 0.25±0.01 | 0.24 | 0.26 |
| Average Constriction velocity (mm/sec) | -3.15±0.73 | 2.71 | 3.59 | -3.06±0.88 | 2.50 | 3.62 |
| Maximum Constriction Velocity (mm/sec) | -4.10±0.91 | 3.55 | 4.65 | -4.07±1.25 | 3.28 | 4.87 |
| Average Dilation Velocity (mm/sec) | 0.87±0.22 | 0.74 | 1.01 | 0.82±0.23* | 0.67 | 0.97 |
| 75% Recovery Time (sec) | 1.78±0.81 | 1.19 | 2.19 | 1.65±0.81 | 1.13 | 2.17 |
| Inflammation index | | | | | | |
| CRP (mg/dl) | 0.53±0.39 | 0.32 | 0.75 | 0.74±0.52* | 0.45 | 1.03 |
| Cognitive function | | | | | | |
| MMSE | 21.46±4.27 | 18.87 | 24.04 | 18.38±4.15* | 15.87 | 20.89 |
| *p<0.05 | | | | | | |

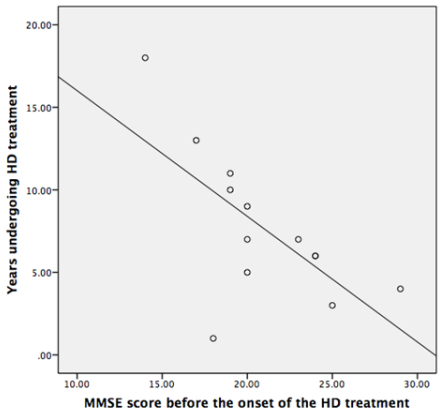


**Figure 1:** Correlation between years undergoing HD treatment and MMSE score before the onset of the HD treatment.

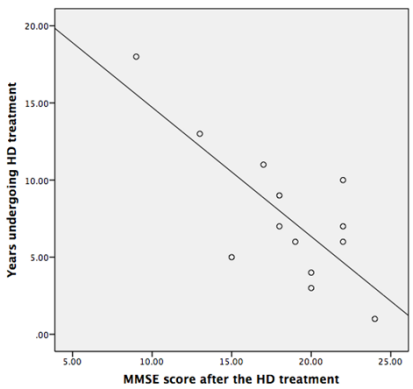


**Figure 2:** Correlation between years undergoing HD treatment and MMSE score after HD treatment.


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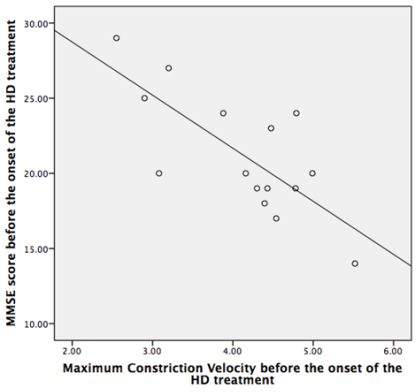


**Figure 3:** Correlation between MMSE score before the onset of the HD treatment and the pupillometric index of maximum constriction velocity.

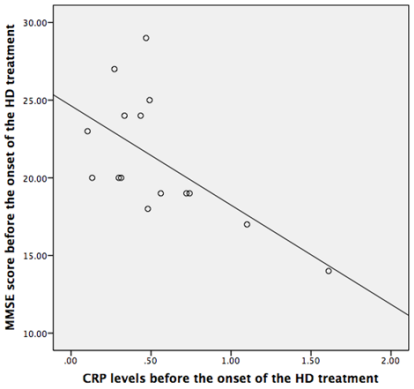


**Figure 4:** Correlation between MMSE score before the onset of the HD treatment and CRP levels.

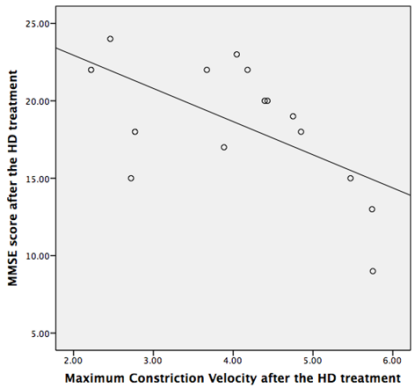


**Figure 5:** Correlation between MMSE score after the HD treatment and the pupillometric index of maximum constriction velocity.

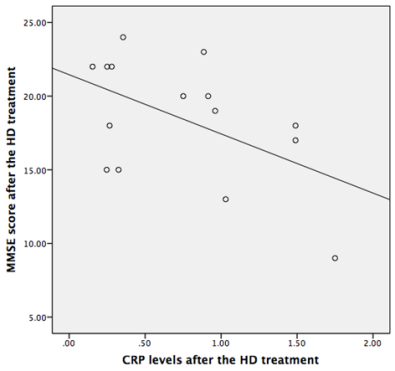


**Figure 6:** Correlation between MMSE score after the HD treatment and CRP levels.

Multiple regression analysis using MMSE score as a subordinate variable (Table 3) revealed that years in HD therapy (p=0.011), Systolic Blood pressure at rest (p=0.021), Diastolic Blood pressure at rest (p=0.031), Maximum Constriction Velocity (p=0.001) and CRP levels (p=0.002) had a significant contribution to the model. The model explained 73.3% of the total variance (F=11.27, $R^2$=0.874). Finally, analysis using the MMSE score after the completion of the HD session as a dependent variable (Table 4), showed that years in HD therapy (p=0.001), Systolic Blood pressure after the completion of the HD session (p=0.018), Diastolic Blood pressure after the completion of the HD session (p=0.005), Maximum Constriction Velocity after the completion of the HD session (p=0.001) and CRP levels after the completion of the HD session (p=0.001) contributed to the model, which explained 67.3% of the total variance (F= 5.27, R2= 0.674).

**Table 3:** Multiple regression analysis with MMSE score before the HD session as the dependent variable.

| | β | P-value |
|---|---|---|
| Years in HD | 9.546 | 0.011* |
| Rest Systolic blood Pressure | -0.409 | 0.021* |
| Rest Diastolic Blood Pressure | 0.173 | 0.031* |
| Rest Heart rate | 0.369 | 0.093 |
| Maximum pupil diameter before the HD session | 6.575 | 0.763 |
| Minimum pupil diameter before the HD session | -0.633 | 0.331 |
| Constriction before the HD session | -0.877 | 0.423 |
| Latency before the HD session | -105.393 | 0.078 |
| Average Constriction velocity before the HD session | -3.205 | 0.211 |
| Maximum Constriction Velocity before the HD session | -2.155 | 0.001* |
| Average Dilation Velocity before the HD session | -3.205 | 0.098 |
| 75% Recovery Time before the HD session | -4.003 | 0.112 |

| | | |
|---|---|---|
| CRP before the HD session | -10.381 | 0.002* |
| *p<0.05 | | |

**Table 4:** Multiple regression analysis with MMSE score after the completion of the HD session, as the dependent variable.

| | β | P-value |
|---|---|---|
| Years in HD | -0.648 | 0.001* |
| Systolic blood Pressure after the completion of the HD therapy | 0.288 | 0.018* |
| Diastolic Blood Pressure after the completion of the HD therapy | 0.111 | 0.005* |
| Heart rate after the completion of the HD therapy | -0.433 | 0.123 |
| Maximum pupil diameter after the HD session | 0.081 | 0.321 |
| Minimum pupil diameter after the completion of the HD session | 6.74 | 0.104 |
| Constriction after the completion of the HD session | 1.062 | 0.278 |
| Latency after the completion of the HD session | -98.348 | 0.311 |
| Average Constriction velocity after the completion of the HD session | -1.69 | 0.453 |
| Maximum Constriction Velocity after the completion of the HD session | -6.604 | 0.001* |
| Average Dilation Velocity after the HD session | -2.324 | 0.111 |
| 75% Recovery Time after the completion of the HD session | -6.095 | 0.507 |
| CRP after the completion of the HD session | 8.063 | 0.001* |
| *p<0.05 | | |

## Discussion

In this study, relationships between inflammation and ANS activity indices on cognitive impairment during a HD session were examined. Our results revealed that after the HD session cognitive function was reduced indicating that HD session has a negative impact on HD patients cognitive performance.

Generally, cognitive function is a multidimensional concept that describes the domains resulting from healthy brain performance [31]. Especially, cognitive function refers to abilities such as perception, memory, verbalizing, and thinking [32] and includes the processes by which an individual perceives, registers, stores, retrieves, and uses information. HD patients have been proved to be more than three times more likely to develop severe cognitive impairment than healthy people [33]. Our results before the HD sessions revealed that CKD patients had mild to moderate cognitive impairment since their score in MMSE were below 24 [23]. These results are in accordance with those observed in a study by Sehgal et al. [4], where recognition and mental impairments were examined with MMSE questionnaire in 336 CKD patients. The authors found that a high percentage of 30% of the participants were mentally impaired and their score in MMSE indicated mild cognitive impairment [4]. In addition in a study by Kurella et al. [2] cognitive impairment was observed in HD patients in executive function and in memory. Thus, cognitive impairment is a common abnormality in HD patients.

After the completion of the 4-hours dialysis session, the participants had decreased cognitive function by 14.3%. However, in a study by Schneider et al. [34], who examined the effects of a single HD session on cognitive performance, found improvements in memory and executive functions and in psychomotor abilities. These results are in contradiction with the results of our study, where after 30 min of HD therapy completion, the cognitive function observed, was impaired. One explanation for this is that in the study by Schneider et al. [34] cognitive function was examined with different tests; specifically a neuropsychological test battery was applied, 1 hour before the onset and 19 hours after the completion of the HD therapy. Moreover, the participants in this study were younger and had been in HD treatment for more years in comparison with those in the study of Schneider et al. [34]. Previous studies have reported that cognitive function was improved 24 hours after the HD therapy and worsened as the time from the last HD session increased [35,36]. A strong relation between cognitive function and GFR has been reported in many studies indicating that as kidney function decreases, cognitive function worsens [2]. Moreover, hemodynamic changes, large fluid shifts and accordingly cerebral ischemia have been suggested to contribute to impaired cognitive function during HD [37].

After the dialysis session, the inflammatory biomarker of CRP increased, indicating that inflammation status worsened. Taking into account that normal values for CRP are between 0-0.5 mg/L in healthy subjects, the fact that the participants had CRP levels above 0.5 mg/L indicates that they were characterized by inflammation. It has been supported that inflammation is implicated in cognitive impairment [38]. Severe or prolonged systemic inflammation can induce harmful changes in cognitive function such as synaptic loss, dendritic alterations, neuronal apoptosis, and suppression of brain-derived neurotrophic factor, impaired neurogenesis, memory dysfunction, and altered hypothalamic function by activating microglia [38]. Indeed, Montinaro et al. [14], who investigated the psychological alterations in HD patients and correlated them with cytokine production, revealed that an association between abnormal cytokine production and the presence of emotional symptoms existed. In this study a negative correlation was observed between cognitive function and levels of the inflammatory biomarker of CRP. Specifically, as the MMSE score worsened the CRP levels increased, indicating that inflammation may play a role in the cognitive function deficit, which characterizes HD patients. However, a study by van den Kommer [39], suggested that inflammation in combination with other risk factors may be implicated in cognitive dysfunction.

In patients with CKD clinical data have showed that altered cardiac autonomic tone remains one of the main reasons for the increased morbidity and mortality rates. Heart rate variability indices, which are accepted tools for the assessment of ANS


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activity, were found to be decreased as a result of a sympathetic overestimation in HD patients [40]. This is correlated with cardiac dysfunction, impaired cardiorespiratory fitness and emotional disturbances, as depression in HD [4,41]. Importantly, there is evidence that there is an association between ANS outflow and various inflammatory indices in patients with septic conditions or cardiac diseases [42,43].

In this study ANS function was examined with the method of pupillometry. After the dialysis session only the index of Maximum Dilation Velocity, which is a marker of sympathovagal balance, was increased. Yamaji et al. [44] divided the characteristic V-shaped pupillometric response into three distinct periods, which reflect different aspects of nervous activity. Therefore, according to Yamaji et al. [44] the first segment of the pupillometric response, is governed exclusively by the parasympathetic branch of the ANS. Accordingly, the second period reflects both types of ANS activity and the third period is controlled only by the sympathetic activity. Therefore, latency and average dilation velocity reflects the sympathovagal balance since they are involved in the second segment of the characteristic V-shaped pupillometric response. Finally, 75% recovery time is governed exclusively by the sympathetic branch of the ANS and is located in the third period of the V-shaped pupillometric response. Our results revealed a negative correlation between Maximum Constriction Velocity, which reflects PNS activity and MMSE score, namely as PNS activity increased, MMSE score was reduced. These results suggest that ANS is implicated in the pathophysiology of cognitive dysfunction and a cholinergic hypofunction occurred like in patients with Alzheimer's disease [19] and Myasthenia Gravis [20].

The results of this study should be interpreted in the face of certain limitations. A main limitation of the study is the absence of long-term follow-up. Moreover, the quality of each dialysis session was not assessed. Finally, the small number of the patients is another limitation.

Thus, treating inflammation and ANS dysfunction, may contribute to the better management of the cognitive impairment, commonly detected in HD patients. Strategies for improving cognitive function will also have an important impact on HD patients' management, quality of life and prognosis. In clinical practice, implementing interventions, as exercise training that is found to improve both comorbid conditions may also lead to better cognitive function.

## Ethical Approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number 48279/2016) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Registration Number: ACTRN12616000776404

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