Glasnik hemičara i tehnologa Bosne i Hercegovine

Bulletin of the Chemists and Technologists of Bosnia and Herzegovina

2021

56

Print ISSN: 0367-4444
Online ISSN: 2232-7266

Original Scientific Article
DOI: https://doi.org/10.35666/2232-7266.2021.656.04
UDC: 612.015 : 616.894-052

21-28

Serum levels of non-enzymatic antioxidants in female dementia patients with respect to the degree of cognitive impairment

Lepara, O.[a], Ibragić, S.[b*], Rebić, D.[c], Zukić, E.[d], Krupić, F.[e], Džubur, A.[f], Fajkić, A.[g], Pepić, E.[g], Novaković, A.[d], Gojak R.[h]

[a]*Department of Human Physiology, University of Sarajevo School of Medicine, Čekaluša 90, Sarajevo, B&H*

[b]*Department of Chemistry, Faculty of Science, University of Sarajevo, Zmaja od Bosne 33-35, Sarajevo, B&H*

[c] *Clinic for Nephrology, University Clinical Centre of Sarajevo, Bolnička 25, Sarajevo, B&H*

[d]*Primary Health Care Center Gornji Vakuf-Uskoplje, Bistrička cesta bb, Gornji Vakuf-Uskoplje, B&H*

[e]*Department of Anesthesiology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Department of Orthopaedics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Universitetsplatsen 1, Gothenburg, Sweden*

[f]*Department for Cardiology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Center University of Sarajevo, Bolnička 25, Sarajevo, B&H*

[g]*Department of Pathophysiology, University of Sarajevo School of Medicine, Čekaluša 90, Sarajevo, B&H*

[h]*Clinic of Infectious Disease, University Clinical Center Sarajevo, Bolnička 25, Sarajevo, B&H*

Article info
Received: 19/10/2020
Accepted: 09/02/2021

Keywords:
Cognition
Oxidative Stress
Bilirubin
Uric Acid
Serum Albumin

***Corresponding author:**
Saida Ibragić
E-mail: saidetun19@gmail.com
Phone: 00-387 33 279914

Abstract: The aim of this study was to investigate the correlation between the severity of cognitive impairment in Alzheimer's disease (AD) and vascular dementia (VD) and the serum antioxidant status of uric acid (UA), albumin (ALB) and bilirubin (BIL) in female patients. The cross-sectional study included 90 subjects, aged ≥65, divided into three groups: 30 patients with AD, 30 patients with VD and 30 control subjects. For cognitive assessment, all participants underwent the Montreal Cognitive Assessment (MoCA). Serum concentrations of ALB, UA and BIL were determined spectrophotometrically. The AD patients had a significant decrease of UA and increase of serum BIL. Upon stratification according to the degree of cognitive impairment, lower UA concentrations were found in patients with severe cognitive impairment, whereas increased BIL was found in patients with moderate cognitive impairment. Patients with VD were characterized by hypoalbuminemia and upon stratification this finding was evident among patients with severe cognitive impairment. The MoCA score correlated positively with BIL in AD patients. The obtained data supports the protective role of serum antioxidants in the pathogenesis of dementia. Further on, we suggest further longitudinal research to confirm the combined use of these parameters as potential biomarkers in AD and VD.

INTRODUCTION

The causes of dementia are still incompletely understood, but it is certain that the accumulation of reactive oxygen species results in the damage of brain cellular structures. Low content of antioxidants, the abundance of polyunsaturated fatty acids, and high oxygen consumption are the main predispositions of brain tissue vulnerability towards oxidative damage (Wang and Michaelis, 2010). Alzheimer's disease (AD)

and vascular dementia (VD) are the two most common types of dementia that affect physiological, cognitive, and behavioral functions in the elderly population. The burden these diseases place on patients and society urge for the identification of risk factors and preventive strategies.Plasma systemic antioxidants, including homocysteine, UA, albumin ALB and BIL, are strong free radicals scavengers and hence described as non-enzymatic laboratory parameters associated with oxidative stress (Wayner, Burton, Ingold et al., 1987; Cascalheira, João, Pinhanços *et al.*, 2009). The antioxidant functions of serum albumin are related to its chemical structure that conveys ligand-binding and free radical-trapping properties (Halliwell and Gutteridge, 2015). The hydrophilic UA is known for suppressing $O_2^{\cdot-}$ and $^1O_2$ and protecting ascorbic acid from oxidation through metal chelation (Waugh, 2008). On the other hand, bilirubin's lipophilic nature makes it effective against some lipophilic reactive oxygen species (Kim and Park, 2102). As a cytotoxic waste product and the end product of heme metabolism, bilirubin is, therefore, an important antioxidant, which has anti-inflammatory and immunosuppressive properties, too (Jangi, Otterbein and Robson, 2013). While the antioxidant activities of UA, ALB, and BIL are universally acknowledged, recent studies have produced equivocal or conflicting results regarding their association with cognitive impairment. It is partially due to the concentrations achieved in biological fluids and the fact that different biological activities may depend on the chemical microenvironment. In addition, it appears that a single serum antioxidant may exhibit different roles, depending on the type of dementia. The aim of the study was to investigate serum levels of non-enzymatic antioxidants in female patients with AD and VD. To the best of our knowledge, this is the first study of this kind in our country. In clinical practice, serum levels of ALB, BIL and UA are routinely measured, however our aim was to determine whether there was an association between their serum levels and cognitive impairment in these patients.

EXPERIMENTAL

Patients and study design

This controlled, cross-sectional study included 90 female subjects, aged ≥65, divided into three groups: 30 patients with AD, 30 patients with VD and 30 control subjects. The study was designed to include female patients only to exclude the influence of gender on the study results but also due to the low prevalence of male patients**.** Patients were recruited from a specialized unit at the Health-Care Hospice for persons with disabilities in Sarajevo, B&H, and their baseline characteristics are presented in Table 1. Subjects diagnosed with AD met the NINCDS-ADRDA criteria (McKhann, Drachman, Folstein *et al.*, 1984) and subjects diagnosed with VD met the NINDS-AIREN criteria (Román, Tatemichi, Erkinjuntti *et al.*, 1993). For the differentiation between AD and VD patients, the Hachinski ischemic score (HIS) was used (Lončarević, Mehmedika-Suljić, Alajbegović *et al.*, 2005). For cognitive assessment, all participants underwent the Montreal Cognitive Assessment (MoCA). All subjects in the AD and VD groups had a score ≤20, while the control group (CG) subjects had a score between 27 and 30. The patients with AD and VD were further classified as those with severe cognitive impairment (MoCA score: <10) and moderate cognitive impairment (MoCA score: 10-17) (Claveau, Presse, Kergoat *et al.*, 2018).

The exclusion criteria were chronic inflammatory diseases (asthma and rheumatoid arthritis), hepatic or renal insufficiency and cancer.

The study was approved by the local research Ethics Committee (protocol number 0305-28838) and conducted according to the Helsinki Declaration of 2013. Informed consent was obtained from caregivers for the dementia patients upon careful explanation of the study procedure. The control subjects were also explained the study procedure and they all signed the inform consent.

METHODS

After overnight fasting, venous blood samples were drawn from the median cubital vein, allowed to coagulate and centrifuged (5 min, 2000 g). The serum samples were stored and frozen at -80°C until analysis.

Serum concentrations of ALB (reference range 35-50 g/L), UA (reference range 155-428 μmol/L) and BIL (reference range 1.7-20.5 μmol/L) were determined on automated apparatus (Cobas 600 Roche Hitachi) at the Clinical Centre of the University of Sarajevo, Laboratory for clinical chemistry and biochemistry, using standard spectrophotometric methods.

Statistical Analysis

Statistical analysis was performed using the SPSS 16.0 software. The distribution of variables was tested by the Shapiro-Wilk test. Values with normal distribution were expressed as mean ± standard deviation, while those without normal distribution were shown as median and interquartile range. Depending on the distribution of variables, a comparison between the groups was performed by the ANOVA test Bonferroni post hoc test and Kruskal–Wallis test followed by Mann-Whitney U-test. Additionally, since variables were not normally distributed, correlations were assessed by Spearman's test. Multiple linear regression was used to assess antioxidants as predictors of the MoCA score in all patients.

To determine optimal cutoff values of potential biomarkers for differentiation between AD patients and CG, as well as for differentiation of patients with VD and CG, receiver operating characteristic (ROC) curves and their corresponding areas under the curve (AUC) were used. The accuracy rate for ROC curves was calculated with a 95% confidence interval (95% CI). Statistical significance was set at $p < 0.05$.

RESULTS

The baseline characteristics of the three study groups are shown in Table 1. There were no differences in age, systolic and diastolic blood pressures, WHR and BMI between the groups (Table 1).

Table 1. Baseline characteristics of patients with AD or VD and the control group.

Variables	CG (n=30)	AD group (n=30)	VD group (n=30)
Age (years)	80.5 (77.75-83.0)	82.5 (79.75-87.0)	79.0 (76.75-87.0)
BMI (kg/m^2)	26.18 ± 4.25	24.79 ± 3.69	24.76 ± 5.92
WHR	0,89 (0,87-0.91)	0,88 (0,83-0,92)	0,90 (0,86-0,93)
SBD (mmHg)	132.5 (125.0-152.5)	135.0 (115.0-150.0)	130.0 (120.0-140.0)
DBP (mmHg)	85.0 (70.0-90.0)	80.0 (70.0-90.0)	82.5 (75.0-90.0)

Data as mean ± SD and as median and interquartile range. AD: Alzheimer's disease; VD: Vascular dementia; BMI: Body mass index. WHR: Waist-Hip Ratio. SBP: systolic blood pressure; DBP: diastolic blood pressure

Patients with AD had significantly lower UA and significantly higher BIL concentrations compared to controls. Such differences were not evident among patients with VD. The only statistically significant difference regarding ALB concentrations were its lower values in VD patients compared with controls. Uric acid and BIL concentrations were also significantly different between the two groups of dementia patients (Table 2).

Table 2. Serum concentrations of non-enzymatic antioxidants in patients with dementia and the control group

Parameter	CG (n=30)	AD group (n=30)	VD group (n=30)
Uric acid (μmol/L)	353.50 (265.00-535.00)	253.00 * (193.75-362.00)	324.50 $^{\#}$(236.25-503.50)
Albumin (g/L)	37.13±0.84	35.23±0.71	34.33±0.98 *
Bilirubin (μmol/L)	5.65 (4.67-6.70)	6.65 *(5.25-8.82)	5.30 $^{\#}$(4.25-7.37)

CG, control group; AD group, patients with Alzheimer's disease; VD group, patients with vascular dementia; *p<0.05, in comparison to the CG; $^{\#}$p<0.05, in comparison to the AD group

Optimal cutoff values, area under the curve (AUC), sensitivity, specificity, positive and negative predictive value of serum antioxidants in for differentiation purposes are presented in Table 3. Results regarding the correlation between serum non-enzymatic antioxidants and MoCA in patients with dementia and the CG showed a statistically significant positive correlation in the case of BIL in patients with AD (Rho=0.375; p<0.05). The multiple linear regression model that included all non-enzymatic parameters and confusing variables, did not reveal any significant predictors of the cognitive MoCA score in AD and VD patients.

The differences in non-enzymatic antioxidants were further evaluated upon stratifying the dementia diseases into degrees of moderate and severe cognitive impairment (Table 4). The serum UA concentrations were significantly lower in the AD group with severe cognitive impairment compared to the AD group with moderate cognitive impairment and compared to the CG, but no significant difference in UA levels was found between AD patients with moderate cognitive impairment and CG. There were no differences in ALB concentrations between the groups. The serum BIL concentrations were significantly higher in the AD group with moderate cognitive impairment compared to the AD group with severe cognitive impairment and compared to the CG, but no significant difference in BIL levels was found between AD patients with severe cognitive impairment and CG.

The only statistically significant difference in serum ALB concentrations was found between patients with severe cognitive impairment in comparison to the CG (Table 5.)

Table 3. Optimal Cut-off, Area under the curve (AUC), sensitivity, specificity, positive and negative predictive value of serum non-enzymatic antioxidants in differentiating between AD patients and control subjects, as well as in differentiating between AD and VD patients.

Parameter	Optimal Cut off (μmol/L)	AUC (95% CI)	SEN	SPE	PPV	NPV	p
Uric acid AD *vs.* CG	≥ 310.50	0.723 (0.594-0.851)	66.7	73.3	71.4	68.8	0.003
Bilirubin AD *vs.* CG	≥ 7.05	0.665 (0.528-0.802)	46.7	83.3	73.7	60.9	0.028
Bilirubin AD *vs.* VD	≥ 6.25	0.671 (0.534-0.808)	60.0	66.6	64.2	62.5	0.023

AD, patients with Alzheimer's disease; VD, patients with vascular dementia; CG, control group; AUC, area under curve; CI, Confidence interval; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value

Table 4. Serum non-enzymatic antioxidant concentrations in patients with AD stratified according to the degree of cognitive impairment and in control subjects

Parameter	CG (n=30)	AD group with severe cognitive impairment (n=19)	AD group with moderate cognitive impairment (n=11)
Uric acid (μmol/L)	353.50 (265.00-535.00)	215 *(151-305)	300 $^{\#}$(259-408)
Albumin (g/L)	37.13±0.84	34.84±0.90	35.90±1.19
Bilirubin (μmol/L)	5.65 (4.67-6.70)	6.1 (4.8-7.1)	7.6 * $^{\#}$(7.2-12.5)

CG, control group; VD group, vascular dementia, *p <0.05 - in comparison to the CG; $^{\#}$p<0.05 in comparison to the AD group with severe cognitive impairment

Table 5. Serum non-enzymatic antioxidant concentrations in patients with VD stratified according to the degree of cognitive impairment and in control subjects

Parameter	CG (n=30)	VD group with severe cognitive impairment (n=11)	VD group with moderate cognitive impairment (n=19)
Uric acid (μmol/L)	353.50 (265.00-535.00)	314 (231-387)	390 (275-509)
Albumin (g/L)	37.13±0.84	32.81±1.89 *	35.21±1.09
Bilirubin (μmol/L)	5.65 (4.67-6.70)	5.7 (4.1-8.5)	4.9 (4.3-7.3)

CG, control group; VD group, vascular dementia; *p<0.05 - in comparison to the CG

DISCUSSION

The obtained results showed a significant decrease in UA and a significant increase of BIL in AD patients compared to controls. The same trend was observed upon stratification of cognitive impairment, whereby UA was decreased in severe cognitive impairment, and increased levels of BIL were noted in moderate cognitive impairment. In all cases, the UA and BIL levels significantly differed between the two degrees of cognitive impairment. The clinical significance of serum UA is still debated. Many studies have reported decreased UA concentrations in AD patients (Cankurtaran, Yesil, Kuyumcu *et al.*, 2013; Euser, Hofman, Westendorp *et al.*, 2009). Particularly comprehensive was a large cohort study by Euser *et al.* (2009), who concluded that elevated UA reduced dementia risk, independent of the cardiovascular risk. The study of Hong, Lan, Tang *et al.* (2015) included 28760 gouty patients with both non-vascular and VD. After age, gender, and comorbidities adjustment, subjects with hyperuricemia were found to be at lower risk of non-vascular dementia, including AD (Tana, Ticinesi, Prati *et al.*, 2018). Our results are in line with these studies; however, there were also a few reports which imply a significant association between UA and white matter atrophy (Verhaaren, Vernooij, Dehghan *et al.*, 2013) or even no significant difference of UA values between AD patients and controls (Chen, Guo, Huang *et al.*, 2014). The biosynthetic pathways are the reason why UA is considered both as potentially neuroprotective and as potentially damaging. Depending on the concentration in the cerebrospinal fluid and the chemical micro-environment, UA may have detrimental effects (Desideri, Gentile, Antonosante *et al.*, 2017).

Unlike AD, the correlation between UA and VD is more precise. By accelerating vascular diseases, UA could contribute to cognitive decline (Vannorsdall, Jinnah, Gordon *et al.*, 2008). One study showed that elevated serum UA could lead to inflammation and oxidative stress processes, resulting in severe atherosclerosis, cerebral ischemia, and hypoxia, thereby increasing the risk for cognitive impairment in female patients (Perna, Mons, Schöttker *et al.*, 2016). Collectively, recent

research data suggest that serum UA may have different physio-pathological roles and clinical utility, depending on the type of dementia.

Bilirubin, the second parameter of this study that showed a significant difference between AD patients and controls, has been reported to have more potent antioxidant activity than α-tocopherol, superoxide dismutase and catalase (Stocker, Yamamoto, McDonagh *et al.*, 1987). Impaired liver functions are common in older adults and AD patients. These alterations, including changes in BIL metabolism, have been widely observed; however, the exact association with AD pathogenesis is insufficiently elucidated (Grimm, Zimmer, Lehmann *et al.*, 2013). Still, several authors (Cankurtaran *et al.*, 2013; Kim, Pae, Yoon *et al.*, 2006) observed lower BIL levels in AD patients. On the other hand, using an animal model, Chen, Liang, Xu *et al.* (2019) provided evidence that strengthens BIL as an endogenous pathogenic factor of AD. This is in agreement with our results that have shown increased levels of BIL in female patients with AD. The same authors postulated that neuronal BIL may be increased by low serum ALB concentration, hyperbilirubinemia and abnormally increased permeability of the blood brain barrier. In the present study, the MoCA score was correlated with all three oxidative stress parameters, but a positive correlation was established for BIL only. Vasantharekha, Priyanka, Swarnalingam *et al.* (2017) also found a positive correlation between cognitive function and BIL. However, the same study reported a decline in BIL concentrations in AD patients. Similarly, de Leeuw, van der Flier, Tijms *et al.* (2020) conducted a study where low bilirubin and zinc levels were associated with cognitive decline.

According to the obtained results, serum ALB concentrations were significantly decreased in VD patients, but not in AD patients. Upon stratifying the degree of cognitive impairment, a significant reduction in ALB content was evident only among patients with severe cognitive impairment. The ALB concentrations did not differ significantly between the groups of VD patients with moderate and severe cognitive impairment. Lower ALB concentrations imply impaired blood supply to the central nervous system and imbalance in the redox system - predispositions for cognitive impairment (Mao, 2013). Hypoalbuminemia was reported to be independently associated with poor cognitive performance and dementia in the elderly by several authors (Duarte, Duarte, Pelichek *et al.*, 2017; Murayama, Shinkai, Nishi *et al.*, 2017). We classify our finding of decreased ALB concentrations in VD patients as expected considering the ALB roles mentioned above and studies which reported an association between hypoalbuminemia and increased risk of coronary heart disease and venous thromboembolism (Vázquez-Oliva G, Zamora A, Ramos *et al.*, 2018; Kunutsor, Seidu, Katechia *et al.*, 2018). A highly important role of ALB is the ability to inhibit the formation of amyloid beta-peptide fibrils (Milojevic, Esposito, Das *et al.*, 2007). That is the reason why low levels of ALB in the brain and cerebrospinal fluid may lead to increased Alzheimer's type pathology (Galeazzi, Galeazzi, Valli *et al.*, 2002). Our results also showed decreased serum ALB concentrations in AD patients compared to controls; however, the difference was of no statistical significance. Albumin could not be considered as a specific biomarker of cognitive decline since minor to severe hypoalbuminemia is observed in common geriatric diseases. As a single parameter, it does not provide substantial assistance in the differential diagnosis, but rather perhaps, in conjunction with other antioxidant parameters.

The main limitation of this study was the cross-sectional design with a rather small sample size that did not assess the nutritional and educational status of the female subjects. While the exact mechanistic role of various antioxidants and their interplay in the pathogenesis of dementia diseases is still obscure, our results indicate that antioxidant deficiencies pose a risk for cognitive decline. The novelty of this study is reflected in the comparison of several non-enzymatic antioxidants in female patients with AD and VD and their evaluation according to the level of cognitive impairment. These parameters can be used as predictive tools in the progression of dementia diseases. Prospective studies with a larger cohort would be required to verify the suggested utility.

CONCLUSION

Patients with VD have significantly lower ALB concentrations. Upon stratification, according to the degree of cognitive impairment, a decline in concentrations of ALB and UA was found in patients with dementia with severe cognitive impairment. Such a finding can be attributed to their consumption in defense against the damage caused by free radicals reactions. On the other hand, BIL was increased in patients with AD, and its concentration was positively correlated to the MoCA score. In summary, the obtained data support the hypothesis that there is an association between natural oxidative and antioxidant markers and the type of dementia.

REFERENCES

Cankurtaran, M., Yesil, Y., Kuyumcu, M. E., Oztürk, Z. A., Yavuz, B. B., Halil, M., Ulger, Z, Cankurtaran, E. S., Arıoğul,, S. (2013). Altered levels of homocysteine and serum natural antioxidants links oxidative damage to Alzheimer's disease. *Journal of Alzheimer's Disease*, *33*(4), 1051-1058.

Cascalheira, J. F., João, S. S., Pinhanços, S. S., Castro, R., Palmeira, M., Almeida, S., Faria, M. C., Domingues, F. C. (2009). Serum homocysteine: interplay with other circulating and genetic factors in association to Alzheimer's type dementia. *Clinical biochemistry*, *42*(9), 783-790.

Chen, H., Liang, L., Xu, H., Xu, J., Yao, L., Li, Y., Tan, Y., Li, X., Huang, Q., Yang, Z., Wu, J. (2019). Short Term Exposure to Bilirubin Induces Encephalopathy Similar to Alzheimer's Disease in Late Life. *Journal of Alzheimer's Disease*, (Preprint), 1-19.

Chen, X., Guo, X., Huang, R., Chen, Y., Zheng, Z., Shang, H. (2014). Serum uric acid levels in patients

with Alzheimer's disease: a meta-analysis. *PloS one*, *9*(4), e94084.

Claveau, J. S., Presse, N., Kergoat, M. J., Villalpando, J. M. (2018). The lost years: delay between the onset of cognitive symptoms and clinical assessment at a memory clinic. *Canadian Geriatrics Journal*, *21*(2), 152.

de Leeuw, F. A., van der Flier, W. M., Tijms, B. M., Scheltens, P., Mendes, V. M., Manadas, B., Bierau, J., van Wijk, N., van den Heuvel, E. G., Mohajeri, M. H., Teunissen, C. E. (2020). Specific Nutritional Biomarker Profiles in Mild Cognitive Impairment and Subjective Cognitive Decline Are Associated With Clinical Progression: The NUDAD Project. *Journal of the American Medical Directors Association*.

Desideri, G., Gentile, R., Antonosante, A., Benedetti, E., Grassi, D., Cristiano, L., Manocchio, A., Selli, S., Ippoliti, R., Ferri, C., Borghi, C., Giordano, A., Cimini, A. (2017). Uric acid amplifies Aβ amyloid effects involved in the cognitive dysfunction/dementia: evidences from an experimental model in vitro. *Journal of Cellular Physiology*, *232*(5), 1069-1078.

Duarte, P. D. O., Duarte, M. G., Pelichek, A., Pfrimer, K., Ferriolli, E., Moriguti, J. C., Lima, N. K. (2017). Cardiovascular risk factors and inflammatory activity among centenarians with and without dementia. *Aging clinical and experimental research*, *29*(3), 411-417.

Euser, S. M., Hofman, A., Westendorp, R. G. J., Breteler, M. M. (2009). Serum uric acid and cognitive function and dementia. *Brain*, *132*(2), 377-382.

Galeazzi, L., Galeazzi, R., Valli, M. B., Corder, E. H., Giunta, S. (2002). Albumin protects human red blood cells against Aβ25–35-induced lysis more effectively than ApoE. *Neuroreport*, *13*(16), 2149-2154.

Grimm, M. O., Zimmer, V. C., Lehmann, J., Grimm, H. S., Hartmann, T. (2013). The impact of cholesterol, DHA, and sphingolipids on Alzheimer's disease. *BioMed research international*, *2013*.

Halliwell, B., Gutteridge, J. M. (2015). *Free radicals in biology and medicine*. Oxford University Press, USA.

Hong, J. Y., Lan, T. Y., Tang, G. J., Tang, C. H., Chen, T. J., Lin, H. Y. (2015). Gout and the risk of dementia: a nationwide population-based cohort study. *Arthritis Research & Therapy*, *17*(1), 139.

Jangi, S., Otterbein, L., Robson, S. (2013). The molecular basis for the immunomodulatory activities of unconjugated bilirubin. *The International Journal of Biochemistry & Cell Biology*, *45*(12), 2843-2851.

Kim, S. Y., Park, S. C. (2012). Physiological antioxidative network of the bilirubin system in aging and age-related diseases. *Frontiers in pharmacology*, *3*, 45.

Kim, T. S., Pae, C. U., Yoon, S. J., Jang, W. Y., Lee, N. J., Kim, J. J., Lee, S. J., Lee, C., Paik, I. H., Lee, C. U. (2006). Decreased plasma antioxidants in patients with Alzheimer's disease. *International journal of geriatric psychiatry*, *21*(4), 344-348.

Kunutsor, S. K., Seidu, S., Katechia, D. T., Laukkanen, J. A. (2018). Inverse association between serum albumin and future risk of venous thromboembolism: interrelationship with high sensitivity C-reactive protein. *Annals of medicine*, *50*(3), 240-248.

Loncarević, N., Mehmedika-Sulić, E., Alajbegović, A., Kucukalić, A. (2005). The neurologist role in diagnostics and therapy of the Alzheimer's disease. *Medicinski Arhiv*, *59*(2), 106-109.

Mao, P. (2013). Oxidative stress and its clinical applications in dementia. *Journal of Neurodegenerative Diseases*, *2013*.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939-939.

Milojevic, J., Esposito, V., Das, R., Melacini, G. (2007). Understanding the molecular basis for the inhibition of the Alzheimer's Aβ-peptide oligomerization by human serum albumin using saturation transfer difference and off-resonance relaxation NMR spectroscopy.*Journal of the American Chemical Society*,*129*(14), 4282-4290.

Murayama, H., Shinkai, S., Nishi, M., Taniguchi, Y., Amano, H., Seino, S., Yokoyama, Y., Yoshida, H., Fujiwara, Y., Ito, H. (2017). Albumin, Hemoglobin, and the Trajectory of Cognitive Function in Community-Dwelling Older Japanese: A 13-Year Longitudinal Study. *The journal of prevention of Alzheimer's disease*, *4*(2), 93-99.

Perna, L., Mons, U., Schöttker, B., Brenner, H. (2016). Association of cognitive function and serum uric acid: are cardiovascular diseases a mediator among women? *Experimental gerontology*, *81*, 37-41.

Román, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., Amaducci, L., Orgogozo, J. M., Brun, A., Hofman, A., Moody, D. M., O'Brien, M. D., Yamaguchi, T., Grafman, J., Drayer, B. P., Bennett, D. A., Fisher, M., Ogata, J., Kokmen, E., Bermejo, F., Wolf, P. A., Gorelick, P. B., Bick, K. L., Pajeau, A. K., Bell, M. A., DeCarli, C., Culebras, A., Korczyn, A. D., Bogousslavsky, J., Hartmann, A., Scheinberg, P. (1993). Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*, *43*(2), 250-250.

Stocker, R., Yamamoto, Y., McDonagh, A. F., Glazer, A. N., Ames, B. N. (1987). Bilirubin is an antioxidant of possible physiological importance. *Science*, *235*(4792), 1043-1046.

Tana, C., Ticinesi, A., Prati, B., Nouvenne, A., Meschi, T. (2018). Uric acid and cognitive function in older individuals. *Nutrients*, *10*(8), 975.

Vannorsdall, T. D., Jinnah, H. A., Gordon, B., Kraut, M., Schretlen, D. J. (2008). Cerebral ischemia mediates the effect of serum uric acid on cognitive function. *Stroke; a journal of cerebral circulation*, *39*(12), 3418.

Vasantharekha, R., Priyanka, H. P., Swarnalingam, T., Srinivasan, A. V., ThyagaRajan, S. (2017). Interrelationship between Mini-Mental State Examination scores and biochemical parameters in patients with mild cognitive impairment and Alzheimer's disease. *Geriatrics & gerontology international*, *17*(10), 1737-1745.

Vázquez-Oliva, G., Zamora, A., Ramos, R., Subirana, I., Grau, M., Dégano, I. R., Muñoz, D., Fitó, M., Elosua, R., Marrugat, J. (2018). Analysis of plasma albumin,

vitamin D, and apolipoproteins A and B as predictive coronary risk biomarkers in the REGICOR study. *Revista Española de Cardiología (English Edition)*, *71*(11), 910-916.

Verhaaren, B. F., Vernooij, M. W., Dehghan, A., Vrooman, H. A., De Boer, R., Hofman, A., Witteman, J. C. M., Niessen, W. J., Breteler, M. M. B., van der Lugt, A., Ikram, M. A. (2013). The relation of uric acid to brain atrophy and cognition: the Rotterdam Scan Study. *Neuroepidemiology*, *41*(1), 29-34.

Wang, X., Michaelis, E. K. (2010). Selective neuronal vulnerability to oxidative stress in the brain. *Frontiers in aging neuroscience*, *2*, 12.

Waugh, W. H. (2008). Inhibition of iron-catalyzed oxidations by attainable uric acid and ascorbic acid levels: therapeutic implications for Alzheimer's disease and late cognitive impairment. *Gerontology*, *54*(4), 238-243.

Wayner, D. D. M., Burton, G. W., Ingold, K. U., Barclay, L. R. C., Locke, S. J. (1987). The relative contributions of vitamin E, urate, ascorbate and proteins to the total peroxyl radical-trapping antioxidant activity of human blood plasma. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *924*(3), 408-419.

Summary/Sažetak

Cilj ovog rada je bilo istražiti korelaciju između stepena kognitivnog oštećenja kod pacijenata ženskog spola oboljelih od Alzheimerove bolesti (AD) i vaskularne demencije (VD), te serumske koncentracije mokraćne kiseline (UA), albumina (ALB) i bilirubina (BIL). Presječna studija je obuhvatala 90 ispitanika, starosne dobi ≥65 godina podijeljenih u tri grupe: 30 pacijenata sa AD, 30 pacijenata sa VD i 30 kontrolnih ispitanika. Za procjenu kognitivnih sposobnosti svi ispitanici su podvrgnuti Montreal Cognitive Assessment testu (MoCA). Serumske koncntracije ALB, UA I BIL su određene spektrofotometrijskim metodama. Pacijenti sa AD su imali značajno niže serumske koncentracije UA, te povišene koncentracije BIL. Nakon stratifikacije prema stepenu kognitivnog oštećenja, niže UA koncentracije su zabilježene kod pacijenata sa teškim kognitivnim oštećenjem, dok je povišen BIL zabilježen kod pacijenata sa umjerenim kognitivnim oštećenjem. Za pacijente sa VD je bio karakteristična hipoalbuminemija, a nakon stratifikacija taj nalaz je bio evidentan kod pacijenata sa teškim kognitivnim oštećenjem. Bodovi MoCA testa su pozitivno korelirali sa BIL kod AD pacijenata. Dobiveni rezultati podržavaju zaštitnu ulogu serumskih antioksidanasa u patogenezi demencije. Nadalje, predlažu se dodatne longitudinalne studije da bi se potvrdila kombinirana upotreba ovih parametara kao potencijalnih biomarkera AD i VD.