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PERIPHERAL 8-ISO-PGF2α AS A BIOMARKER IN BOSNIAN PATIENTS WITH ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA

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SUMMARY

Background: *Cerebrospinal levels of isoprostanes (IsoPs) have been established as biomarkers of oxidative stress in Alzheimer's disease (AD) and vascular dementia (VD). The value of peripheral levels in the diagnostics of these diseases is less conclusive. The aim of this study was to determine serum 8-iso-prostaglandin-F2alpha (8-iso-PGF2α) levels in Bosnian AD and VD patients and to establish whether there is an association between 8-iso-PGF2α serum concentration and cognitive impairment (CI) in patients with dementia.*

Subjects and methods: *Serum levels of 8-iso-PGF2α were measured by enzyme immunoassay method in AD (n=30) and VD patients (n=30) and control subjects (CG, n=30). The AD and VD group were further stratified according to the level of CI.*

Results: *The serum 8-iso-PGF2α levels were significantly higher in the AD (74.00 pg/mL) and VD groups (38.00 pg/mL) compared to the CG (17.50 pg/mL). A significant difference in serum 8-iso-PGF2α levels between patients with moderate and severe CI was not established in either AD or VD.*

Conclusion: *Serum 8-iso-PGF2α proved to be a good biomarker in AD and VD, however it cannot be recommended for the differentiation of moderate and severe CI.*

Key words: *F2-Isoprostanes - oxidative stress - Alzheimer's disease - vascular dementia - cognitive impairment*

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INTRODUCTION

Oxidative stress (OS) is implicated in the ethiopathogensis of multiple diseases including Alzheimer's disease (AD) and vascular dementia (VD). While AD is a neurodegenerative disease, VD is a general term for dementia caused by organic lesions of vascular origin, which can be the result of brain injury produced by cerebrovascular disease or by hypoperfusive lesions resulting from cardiac disease or circulatory failure (Shi et al. 2012). The Aβ protein, total tau (t-tau) and phosphorylated tau (p-tau) proteins are currently the key biomarkers for AD (Radić et al 2019, Eleti 2016), whereas F2-isoprostanes (F2-IsoPs) have gained attention as a reliable marker of oxidation (Wigner et al. 2017, Fiocco et al. 2011). Isoprostanes (IsoPs) are chemically stable, they are specific products of peroxidation, which are produced in vivo and stay detectable in tissues and biofluids. These features of IsoPs reflect why they are preferred over some other markers of oxidative stress (OS) (Czerska et al. 2016). To have clinical utility, a good biomarker should reflect core pathological changes that pertain to the disease process, be validated by postmortem studies, and be sensitive to early changes in the disease process (National Institute on Aging Working Group 1998). The effects of excessive oxidation should be measurable in the blood circulation, provided that OS is one of the main mechanisms behind AD. Studies of cerebrospinal fluid (CSF) levels of F2-IsoPs have shown that levels of F2-IsoPs are characteristically elevated in mild cognitive impairment (MCI), AD dementia, and/or vascular brain injury (VBI) (Sonnen et al. 2008, Bayer-Carter et al. 2011, Seet et al. 2011). Studies that have evaluated peripheral levels of F2-IsoP markers are less consistent. Also, the number of studies assessing F2-IsoP levels in VD is very limited. Hence, the objective of this work was to evaluate serum F2-IsoP levels as a peripheral biomarker in clinical diagnostics of dementia and the severity of CI.

SUBJECTS AND METHODS

Subjects

A controlled, cross-sectional study was performed with 30 patients with possible AD, 30 patients with possible VD and 30 control subjects that were community-dwelling, apparently healthy, asymptomatic individuals. All subjects were female, aged 65 years or over. The patients were recruited from a specialized unit at the Health-Care Hospice for persons with disabilities in Sarajevo, Bosnia and Herzegovina. The

clinical diagnosis was made by a senior staff neurologist and psychiatrist according to the NINCDS-ADRDA criteria for possible AD (McKhann et al. 1984) and NINDS-AIREN criteria for possible VD (Román et al. 1993). Approval for the study was obtained from the local research Ethics Committee, protocol number 0305-28838. All procedures on human subjects were performed in the accordance with Helsinki Declaration of 2013. Informed consent was obtained from subjects and caregivers upon careful explanation of the study procedure. Patient anonymity was assured and is preserved.

Prior to the sample collection, medical history (including socio-epidemiologic data, e.g. smoking habits, alcohol consumption) was obtained from all subjects and laboratory and clinical examinations were performed. The body mass index (BMI: kg/m^2) was calculated from direct weight and height measurements for each subject. The blood pressure was measured by trained professionals using a mercury sphygmomanometer. Subjects with a history of chronic inflammatory disease (asthma and rheumatoid arthritis), hepatic or renal insufficiency and cancer were excluded from the study.

The cognitive status of all participants was evaluated using the Mini - Mental State Examination (MMSE), which is the best known and the most often used short screening tool for providing an overall measure of CI in clinical, research and community settings (Arevalo-Rodriguez et al. 2015). The MMSE assesses orientation, short term memory, serial subtraction, constructional capacities and use of language, where a score below 20 indicates dementia. All subjects in the AD and VD groups had a score ≤20, while the control group (CG) subjects had a score between 26 and 30. The patients with AD and VD were further classified as those with severe cognitive impairment (MMSE score: 0-10) and moderate cognitive impairment (MMSE score: 11-20) (Perneczky et al. 2006). For the differentiation between AD and VD patients, the Hachinski ischemic score (HIS) was used. The original scale consists of 13 items; each scale item was assigned a numeric value with double weighting applied to specific clinical features. A score ≥7 implies vascular dementia, a score of 0-4 implies Alzheimer's dementia and a score of 4-7 implies mixed dementia (Lončarević et al. 2005). Our patients in the AD group had a score ≤4, while the patients with VD had a score ≥7.

Biochemical analysis

After an overnight fasting, in early morning hours, 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 assayed.

The serum 8-iso-PGF2α concentrations were determined using the ELISA method. The assay kit and the instrumentation were as follows: the 8-iso-PGF2α - ELISA kit (Detroit R&D, Inc) and the microplate reader STAT FAX_{2100}, USA. The results were expressed as pg/mL. The measurements were performed at the Department of Physiology and Department of Biochemistry, Faculty of Medicine in Sarajevo, Bosnia and Herzegovina.

Statistical analysis

All statistical calculations were performed with the SPSS 16 software (version 16.0, SPSS Inc, Chicago, Illinois, USA). 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, and Kruskal–Wallis test followed by Mann-Whitney U-test. Additionally, since variables were not normally distributed, correlations were assessed by Spearman's test. To determine optimal cut-off values of 8-iso-PGF2α for differentiation between AD patients and control group (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 95% confidence interval (95% CI). Statistical significance was set at $p<0.05$.

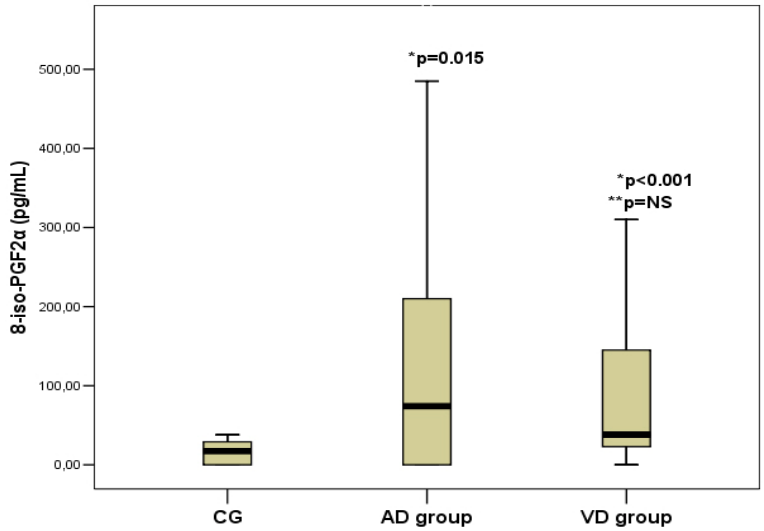
RESULTS

The baseline characteristics of the three study groups are shown in Table 1. There were no differences in systolic and diastolic blood pressures and BMI between the groups. The AD and VD groups had significantly lower MMSE scores than the control group ($p<0.001$), but there was no difference in MMSE scores between the AD and VD groups (Table 1).

Table 1. Baseline characteristics of patients in AD, VD and control group

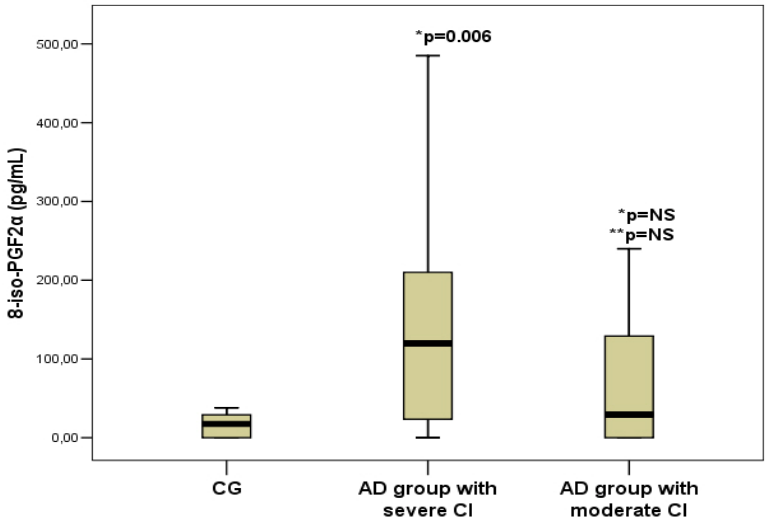
Variables	AD group (n=30)	VD group (n=30)	CG (n=30)
Age (years)	8.76±1.05	80.36±1.14	80.13±1.08
BMI (kg/m^2)	24.81±0.67	24.98±1.09	26.16±0.77
SBD (mmHg)	135.00±0.66	130.83±3.79	134.33±4.18
DBP (mmHg)	80.00±1.79	83.16±2.24	84.16±2.27
MMSE (score)	9.00 (7.00-12.75)*	12.50 (7.00-16.00)*	28.00 (27.00-29.00)

Data as mean ± S.E.M. and as median and interquartile range. AD: Alzheimer's disease; VD: Vascular dementia; CG: control group; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: Body mass index; MMSE: Mini Mental State Examination; * $p<0.001$



CG: control group; AD: Alzheimer's disease; VD: Vascular dementia; CI: cognitive impairment;
*p - in comparison to the CG; **p - in comparison to the AD group with severe CI; NS: not significant

Figure 1. Serum 8-iso-PGF2α concentrations in patients with dementia and in control subjects



CG: control group; AD: Alzheimer's disease; CI: cognitive impairment;
*p - in comparison to the CG; **p - in comparison to the AD group with severe CI; NS: not significant

Figure 2. Serum 8-iso-PGF2α concentrations in patients with AD stratified according to the level of CI and in control subjects

The serum 8-iso-PGF2α concentrations were statistically significantly higher in the AD 74.00 (0.00-212.50) pg/mL and VD groups 38.00 (23.00-146.25) pg/mL compared to the CG 17.50 (0.00-29.25) pg/mL, whereas such a difference was not established between the two disease groups (p=NS) (Figure 1).

As shown in Table 2, the optimal cut-off value of 8-iso-PGF2α determined by ROC curve in differentiating patients with AD vs. CG was ≥28.25 pg/mL. AUC for determined cut-off value was 0.681 with 95% CI of 0.539-0.824 (p=0.016). For a calculated optimal 8-iso-PGF2α cut-off value of ≥28.25 pg/mL, the maximal specificity was 76.7% and maximal sensitivity was 63.6%. Optimal cut-off value of 8-iso-PGF2α determined by ROC curve in differentiating patients with VD vs. CG was ≥31.5 pg/mL. AUC for determined cut-off value was 0.769 with 95% CI of 0.648-0.891 (p<0.001). For a calculated optimal 8-iso-PGF2α cut-off value of ≥31.5 pg/mL, the maximal specificity was 80.0% and maximal sensitivity was 66.7% (Table 2).

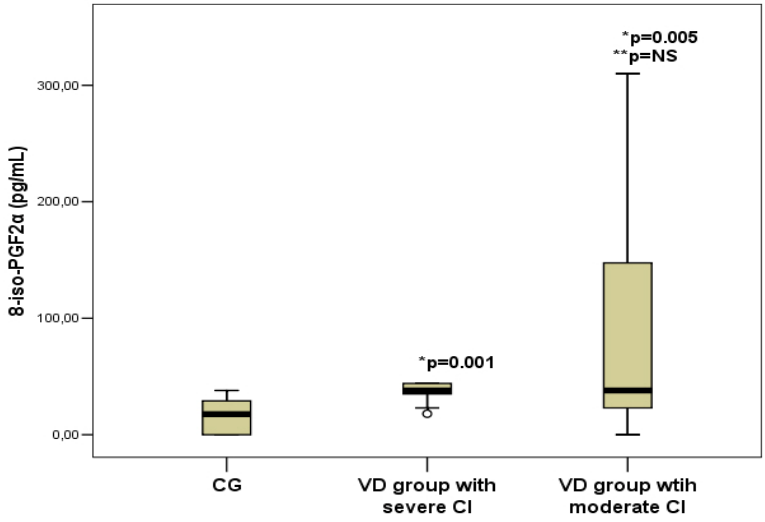
The only statistically significant difference in 8-iso-PGF2α levels in the AD group was found between patients with severe CI in comparison to the CG (120 (18.0-220.0) pg/mL vs. 17.50 (0.00-29.25) pg/mL; p=0.006) (Figure 2).

In case of VD, a statistically significant difference in 8-iso-PGF2α levels was found between patients with both severe (38 (34.0-44.0) pg/mL; (p=0.001)) and moderate (38 (23.0-150.0) pg/mL; (p=0.005)) CI in comparison to the CG (17.50 (0.00-29.25) pg/mL, but no significant difference was found between patients with VD with moderate and severe CI (p=NS) (Figure 3).

Table 2. Optimal Cut-off, Area under the curve (AUC), sensitivity, specificity, positive and negative predictive value of serum 8-iso-PGF2α in differentiating between AD patients and control subjects, as well as in differentiating between VD patients and control subjects

	Optimal Cut off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	p
AD *vs.* CG	(≥28.25 pg/mL)	0.681 (0.539-0.824)	63.3	76.7	73.1	67.7	0.016
VD *vs.* CG	(≥31.5 pg/mL)	0.769 (0.648-0.891)	66.7	80.0	76.9	70.6	<0.001

AD: Alzheimer's disease; VD: Vascular dementia



CG: control group; VD: Vascular dementia; CI: cognitive impairment;
*p - in comparison to the CG; **p - in comparison to the AD group with severe CI; NS: not significant

Figure 3. Serum 8-iso-PGF2α concentrations in patients with VD stratified according to the level of CI and in control subjects

Results showed that there was no statistically significant correlation between the serum 8-iso-PGF2α concentrations and the MMSE scores in any of the investigated groups. Such a correlation was also not found when the patients were stratified by the severity of CI (data not shown).

DISCUSSION

To the best of our knowledge, we are the first to report that serum 8-iso-PGF2α levels were significantly elevated in Bosnian AD and VD patients compared to the CG. Over the past two decades, studies of AD vs controls have produced accumulating evidence that F2-IsoPs (i.e. 8-iso-PGF2α; 8,12-iso-iPF2α-VI) are increased in the CSF (Praticò et al. 2000, Praticò et al. 2002, Montine et al. 2002, Kuo et al. 2015). Such findings are not surprising because CSF closely reflects the composition of the brain extracellular space and is more likely to provide the highest accuracy in biomarker evaluation (Teunissen et al. 2002). Several studies reported that the elevated levels of 8,12-iso-iPF2α-VI in AD patients and patients with MCI not only reflect an increase of central nervous system oxidative stress, which is an early pathological change in AD, but also correlate with the progression of the disease (Praticò et al. 2000, Praticò et al. 2002). Similarly, another study compared baseline and follow up levels of IsoP in the minimum period of 6 months between measurements (Kester et al. 2012). The observed increase was associated with the progression of MCI to AD and with cognitive decline according to changes in the MMSE. Apart from dementia severity, CSF F2-IsoPs have been shown to correlate with brain weight and degree of cortical atrophy (Montine et al. 1999). Further on, in a longitudinal study a larger increase of F2-IsoPs was found over time in the CSF level in APOE-4 carriers than in APOE-4 non-carriers suggesting that APOE status may influence brain's response to oxidative stress (Duits et al. 2013). The F2-IsoP levels in CSF have been shown to correlate well with tau proteins and amyloid (A) β42. In a group of AD patients with increased tau and Aβ42 levels, F2-IsoP levels were found to be significantly higher compared to control subjects and patients with normal tau and Aβ42 levels (Montine et al. 2011). Thus, it was demonstrated that CSF F2-IsoPs may be used in conjunction with CSF Aβ42 and tau to increase the accuracy of laboratory diagnosis of AD. While blood and urine samples are much easier to obtain than CSF, the value of peripheral F2-IsoPs measurements is still unclear. The results are conflicting since several studies reported increased plasma levels in AD (Praticò et al.

2000, Praticò et al. 2002, Şirin et al. 2015) and others reported no significant difference compared to control subjects (Montine et al. 2002, Irizarry et al. 2007). The reasons are manifold and often include different methodology, small sample size, effects of renal metabolism of F2-IsoPs (Montine et al. 2002) and other confounding factors such as diet, exercise, BMI, smoking status and other diseases associated with lipid peroxidation (Basu & Helmersson 2005). When evaluating plasma/ serum levels it is important to consider that those fluids are biochemically complex and as such may dilute brain metabolites and proteins. Further challenges include the short half-life of plasma F2-IsoPs as well as intraday and day-to-day individual variation (Basu & Helmersson 2005). The results of our study have shown that serum 8-iso-PGF2α levels were significantly increased in AD and VD patients but proved insufficient as tools in the differentiation between moderate and severe CI. These findings are in line with the previous studies that were based on smaller sample size where F2-IsoP levels were only indicative of increased OS in plasma of AD patients but ineffective in the stratification of the disease phase (Şirin et al. 2015, Sinem et al. 2010). Similarly, the inability of plasma and urine F2-IsoP levels to differentiate MCI from AD has been reported, too (Mufson & Leurgans 2010). Thus, the accumulated evidence suggests that plasma F2-IsoP levels may not be a sensitive biomarker for the clinical progression of AD. Definite conclusions could be drawn from large prospective studies that asses time-dependent changes in plasma F2-IsoP levels since it is postulated that elevations may occur closer to time of cognitive decline rather than several years prior (Fiocco et al. 2011). Nevertheless, concluding from the obtained results, 8-iso-PGF2α remains a good biomarker of OS. In the case of possible AD, with the sensitivity of 63.3% and the specificity of 76.7%, serum 8-iso-PGF2α levels could be an important biomarker in the diagnostics of this disease.

The 8-iso-PGF2α, have received significant attention because of their vasoconstrictive platelet activation and mitogenic properties. Despite the high prevalence of VD, the number of studies that investigated F2-IsoP as a possible biomarker of that disease is limited. According to one study (Sánchez-Moreno et al. 2004) plasma levels of IsoP were significantly higher among stroke patients than in controls. In the same study, authors observed an inverse correlation between plasma vitamin C concentration and 8-epiPGF2α levels among stroke patients and a positive association between 8-epiPGF2α and C-reactive protein concentrations. These findings led to the conclusion that vitamin C supplementation may have a protective role preventing OS. Our findings showed that serum 8-iso-PGF2α levels were significantly increased in VD and differ from the study that measured 8-iso-PGF2α in urine samples and reported significantly lower levels compared with controls (Shi et al. 2012). Hence, biomarker development in VCI is less mature than in AD and has not yet identified candidates that are ready for standardization and widespread application (Sonnen et al. 2008). Our results suggest that, with the sensitivity of 66.7% and specificity of 80.0% serum 8-iso-PGF2α levels could be a valuable biomarker in the diagnostics of VD.

In interpreting the findings of the current study, several limitations should be acknowledged. Firstly, the sample size was small consisting of patients with AD and VD and control group from select population and, therefore, the results cannot be generalized over the whole population. Secondly, the cross-sectional design of the study prevented us from deducing any causal relations between our findings.

CONCLUSION

Future research remains to elucidate the exact reasons for discrepancies concerning peripheral IsoP and their diagnostic value. However, this study provided additional results supporting the role of 8-iso-PGF2α as a biomarker of oxidative stress in diseases characterized by dementia.

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Conflict of interest: None to declare.

Contribution of individual authors:

Orhan Lepara: obtaining permissions from the Ethics Committee, design of the study, statistical analyses, manuscript writing.

Asija Zaciragic & Almir Fajkic: design of the study.

Alma Dzubur Kulenovic: sample collection, interpretation of data.

Amela Dervisevic: literature searches and analyses, statistical analyses, interpretation of data.

Amina Valjevac: statistical analyses.

Emina Kiseljakovic: bioanalytical measurements (experimental work).

Saida Ibragic: literature searches and analyses, manuscript writing.

All authors approval of the final version.

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