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Lipid peroxidation biomarkers correlation with medial temporal atrophy in early Alzheimer Disease

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ABSTRACT

Alzheimer Disease (AD) is a pathology that causes millions of deaths every year and it also generates severe economic consequences for families and public health systems. Oxidative stress is related to neurodegenerative diseases damage. In fact, brain lipid oxidation could produce brain atrophy. The main objective of this study is the evaluation of atrophy and lipid peroxidation damage in AD patients. We studied medial temporal brain atrophy by magnetic resonance imaging (MRI) and a set of lipid peroxidation biomarkers from plasma samples, respectively. The participants were AD patients in early stages (n = 80) and healthy controls (n = 32). Some lipid peroxidation compounds (neuroprostanes, isoprostanes, neurofurans, isofurans, 17-*epi*-17-F_{2t}-dihomo-IsoP, $PGF_{2\alpha}$) in plasma showed statistically significant correlation with medial temporal atrophy. So, they were selected to generate an AD diagnosis model, showing an AUC-ROC of 0.900, close to accuracy achieved by the model based on neuroimaging analysis (AUC-ROC 0.929). In addition, the new model showed suitable specificity, so it could be used as screening test. The developed model based on plasma biomarkers could reflect white and grey matter lipid peroxidation, which occurs in medial temporal lobe in early AD patients. Nevertheless, more studies are needed in this field in order to evaluate specificity against other dementias or neurodegenerative diseases.

1. Introduction

Alzheimer disease (AD) is the fifth global cause of death according to the World Health Organization (WHO), coming to the third position in high-income countries. In fact, the growing number of death caused by this disease in last years, constitutes a great concern ("World Health Organisation, 2018"). This long progressive pathology involves high costs for families and governments, and the development of new early diagnostic methods and effective treatments are necessary (Alzheimer's Association, 2016).

Clinically, AD is characterized by a cognitive impairment, being memory loss the main symptom. These progressive symptoms are consequences of anatomical alterations in AD patients' brain. The main hallmarks are accumulation of β-amyloid peptides and hyperphosphorylated tau protein, which lead to synapsis loss and degeneration in different brain areas (Kamat et al., 2016). Nowadays, AD diagnosis relies on clinical judgment and exclusion of secondary causes. Diagnosis specificity and certainty, especially in early stages (e.g. mild cognitive impairment (MCI)), can be improved by means of disease biomarkers, such as β-amyloid and tau proteins levels in cerebrospinal fluid (CSF) (Nordberg, 2015). Paying more attention to neuroimaging is useful in AD diagnosis and progression prediction (Rathore et al., 2017) (Sørensen et al., 2017), but sometimes the employment of different image techniques is required to improve their diagnostic capacity (Mi et al., 2017), which increases diagnosis costs (Ramos Bernardes da Silva Filho et al., 2017). Throughout the AD course, different brain areas could be affected (Ferreira et al., 2017). One area with a remarkable atrophy grade during AD progression is the medial temporal lobe, where the hippocampus is located, and this alteration has been used to develop diagnosis models with high reproducibility (Sarria-Estrada et al., 2015). The hippocampus study is even useful in MCI progression prediction (Persson et al., 2017).

Regarding oxidative stress, it is related to AD progression (Pohanka, 2014) and its characteristic synapsis loss since early stages of the disease (Kamat et al., 2016). Actually, it could modify brain proteins and lipids levels, and give place to morphological brain changes (Scheff et al., 2016) (Yadav and Tiwari, 2014) (Klosinski et al., 2015). In this sense, the main objective of this study is to evaluate the correlation

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Abbreviations

AD	Alzheimer Disease
AdA	adrenic acid
AA	arachidonic acid
BBB	blood brain barrier
CDR	Clinical Dementia Rating
CSF	cerebrospinal fluid
DHA	docosahexaenoic acid
DT	difusion tensor
EOAD	Early Onset Alzheimer DIsease
FAQ	Functional Activities Questionnaire
EDTA	ethylenediaminetetraacetic acid
MCI	mild cognitive impairment
MRI	magnetic resonance imaging
MTA	medial temporal atrophy
NIA-AA	National Institute on Aging- NIA-AA - Alzheimer's Association
PET	positron emission tomography
PLS	partial least squares
p-Tau	phosphorylated Tau
RBANS-DM	Repeatable Battery for the Assessment of Neuropsychological Status-Delayed Memory
RLC	relative light changes
ROC	receiver operating characteristic curve
SPE	solid phase extraction
UPLC-MS/MS	ultra-performance liquid chromatography coupled with tandem mass spectrometry
WHO	World Health Organization

between plasma lipid peroxidation biomarkers and anatomical brain changes, specifically medial temporal atrophy.

2. Material and methods

2.1. Participants

Participants between 50 and 80 years old were recruited from de Neurology Unit of the University and Polytechnic Hospital La Fe, Valencia (Spain). Informed consent was approved by the Ethics Committee of the Health Research Institute La Fe (Valencia). Participants were classified in case and control groups according to National Institute on Aging-Alzheimer's Association (NIA-AA) criteria including CSF biomarkers (β-amyloid, Tau and phosphorylate Tau (p-Tau)) and neurophsycological tests (clinical dementia rating (CDR), Functional Activities Questionnaire (FAQ), Repeatable Battery for the Assessment of Neuropsychological Status-Delayed Memory (RBANS-DM), Mini-mental state examination (MMSE)) (McKhann et al., 2011) (Albert et al., 2011). We excluded patients with history of brain structural disease (tumor, stroke, etc), Fazekas score greater than 2, major head trauma, epilepsy, multiple sclerosis and major psychiatric disorders, as well as patients with advanced dementia and patients that were not able to undergo neuropsychological evaluations because of their educational level.

2.2. Sample collection, storage and treatment

Blood samples were taken from all participants using cryo-tubes with ethylenediaminetetraacetic acid (EDTA). They were centrifuged for 10 min at 2000 g and supernatant (plasma) was stored at −80 °C until the analysis. Sample treatment was described in a previous work (Peña-Bautista et al., 2018). Briefly, samples were thawed on ice after adding the internal standard, a basic hydrolysis with potassium hidroxyde and a clean-up step with solid phase extraction (SPE) were carried out. Finally, samples were injected in a chromatographic system and were analyzed by ultra-performance liquid chromatography coupled with tandem mass spectrometry (UPLC-MS/MS) (Peña-Bautista et al., 2018).

CSF samples were obtained as part of the diagnostic protocol in the Polytechnic University Hospital La Fe (Valencia). From 1 to 10 mL of CSF were collected under standardized procedure of lumbar puncture at 8 a.m. after overnight fasting, and they were stored at −80 °C until analysis. Biochemical determinations (β-amyloid, t-Tau, p-Tau) were carried out by Innotest Elisa kit (Fujirebio Diagnostics, Ghent, Belgium) using a fully automated system (Lumipulse G, Fujirebio).

2.3. Neuroimaging data acquisition

Magnetic resonance imaging (MRI) was performed as part of the routine clinical assessment. Images were obtained using three MRI scanners (Siemens): two 1.5 T and one 3T machines were used. Imaging protocol included axial, sagittal and coronal views of the brain using T1, T2, gradient echo and fluid attenuation inversion recovery (FLAIR) sequences. Medial temporal atrophy (MTA) was assessed visually by a single rater relative light changes (RLC) using FLAIR or T1 coronal images at the level of the hippocampus. The visual assessment of MTA was ranged from 0 (no atrophy) to 4 (severe atrophy) and was based on criteria and score system proposed by Scheltens et al. (1992).

2.4. Statistical analysis

First, univariate statistical analysis was carried out using SPSS software version 20.0 (SPSS, Inc., Chicago, IL, USA). The differences between the variables medians of case group and control group were analyzed using the non-parametric Mann Whitney test for numerical variables, and Chi-Square test for nominal variables. Correlations between plasma biomarkers and image data were evaluated by Pearson correlation coefficient (r).

The multivariate statistical analysis was carried out using the Minitab software version 18 (USA). Discriminant analysis was performed by partial least squares regression (PLS). Then, the Receiver operating characteristic curve (ROC) of the discriminant model was obtained. Two models were constructed, the first included plasma biomarkers (isoprostanes, neuroprostanes, isofurans, neurofurans, 17-*epi*-17-F_{2t}-dihomo-IsoP, $PGF_{2\alpha}$), gender and age as predictor variables, and the second included image data (MTA-R (right), MTA-L (left) and MTA-S (sum)), gender and age as predictor variables. The response variable used was group (control-case). All the variables were standardized and cross-validation of the models was carried out. Then diagnosis indices (sensitivity, specificity, positive predictive value, negative predictive value) were calculated for both models.

2.5. Declaration of sources of funding

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3. Results

3.1. Participants' description

In Table 1, demographic and clinical characteristics from the study

Table 1
Demographic and clinical variables for the participants.

Variables	Control (n = 32)	Case (n = 80)	P value
Age (years, median (IQR))	66 (62–69)	71 (68–74)	0.000*
Gender (female, n (%))	11 (34%)	47 (59%)	0.020*
β-amyloid (pg mL^{-1}, median (IQR))	1192 (1051–1444)	588 (441–676)	0.000*
t-Tau (pg mL^{-1}, median (IQR)))	171 (108–284)	523 (361–775)	0.000*
p-Tau (pg mL^{-1}, median (IQR)))	44 (27–57)	82 (66–116)	0.000*
CDR (median (IQR))	0 (0–0)	0.5 (0.5–1)	0.000*
MMSE (median (IQR))	30 (28–30)	22 (18–26)	0.000*
RBANS.DM (median (IQR))	100 (92–106)	44 (40–52)	0.000*
FAQ (median (IQR))	0 (0–0)	7 (3–13)	0.000*
GDS (median (IQR))	3 (1–7)	7 (4–11)	0.021*
Fazekas (median (IQR))	0 (0–1)	1 (0–1)	0.018*
ATM-RIGHT (median (IQR))	0 (0–0)	2 (1–2)	0.000*
ATM-LEFT (median (IQR))	0 (0–0)	1 (1–2)	0.000*
ATM (R + L) (median (IQR))	0 (0–0)	3 (2–4)	0.000*

population are summarized. Age and gender showed statistically significant differences between both groups, so they were included as covariates in the multivariate models. As expected, clinical variables (CSF β-amyloid, CSF Tau, CSF p-Tau, RBANS-DM, CDR, FAQ, MMSE) showed statistically significant differences between case and control groups.

3.2. Image measurement data

Using neuroimaging techniques, the variables determined were MTA-R, MTA-L, MTA-S and Fazekas. As can be seen in Table 2, the three MTA indices showed statistically significant differences between groups, as well as Fazekas.

3.3. Analyte determination

In Table 2 medians of analytes levels determined in plasma from case and control groups are summarized. 8-iso-15(*R*)-$PGF_{2\alpha}$, 2,3-dinor-$iPF_{2\alpha}$-III, 8-iso-15-keto-PGE_2, 4(*RS*)-F_{4t}-NeuroP, neuroprostanes, isoprostanes, Ent-7(*RS*)-F_{2t}-dihomo-IsoP and 17-*epi*-17-F_{2t}-dihomo-IsoP, showed higher levels in the case group than in the control group. Inversely, $PGF_{2\alpha}$, 14(*RS*)-14-F_{4t}-NeuroP, 5-$iPF_{2\alpha}$-VI and 7(*RS*)-*ST*-Δ^8-11-dihomo-IsoF showed higher levels in the control group. Nevertheless, only 8-iso-15(*R*)-$PGF_{2\alpha}$ ($p = 0.042$), $PGF_{2\alpha}$ ($p = 0.001$), 4(*RS*)-F_{4t}-NeuroP ($p = 0.030$), neuroprostanes ($p = 0.001$), isoprostanes ($p = 0.006$) and 17-*epi*-17-F_{2t}-dihomo-IsoP ($p = 0.008$) showed statistically significant differences between groups.

3.4. Correlation between plasma lipid peroxidation biomarkers levels and image indices

Relationship between neuroimaging indices and plasma biomarker levels was analyzed, and some statistically significant correlation was observed. In fact, MTA in right brain lobe showed positive correlation with neuroprostanes ($r = 0.242$, $p = 0.010$), and 17-*epi*-17-F_{2t}-dihomo-IsoP ($r = 0.223$, $p = 0.018$), while it showed negative correlation with $PGF_{2\alpha}$ ($r = -0.259$, $p = 0.006$). Similar results were obtained with MTA in the left side, positive correlation was observed with neuroprostanes ($r = 0.213$, $p = 0.024$), and 17-*epi*-17-F_{2t}-dihomo-IsoP ($r = 0.214$, $p = 0.024$), while it showed negative correlation with $PGF_{2\alpha}$ ($r = -0.305$, $p = 0.001$). In the same sense, the sum of MTA in both brain lobes showed correlation with neuroprostanes ($r = 0.234$, $p = 0.013$), 17-*epi*-17-F_{2t}-dihomo-IsoP ($r = 0.224$, $p = 0.018$) and $PGF_{2\alpha}$ (PCC $= -0.288$, $p = 0.002$). In addition, Fazekas, index related to vascular brain disease, showed correlation with 17-F_{2t}-dihomo-IsoP ($r = 0.215$, $p = 0.023$) (see Fig. 1).

3.5. Multivariate analysis

Two statistical models were carried out, the first based on neuroimaging analysis and the second based on plasma lipid peroxidation biomarkers levels. As it is shown in Fig. 2a, the model based on neuroimaging analysis showed a correlation between the different MTA measures (right and left lobe and total MTA), but age and gender did not correlate with them. Also, the scatter plot (Fig. 2b) showed a satisfactory separation between participants groups. In this sense, the case group is characterized by higher levels of MTA. For this model, the Area under Curve-Receiver Operating Characteristic AUC-ROC is 0.929 (CI 95%, 0.882–0.977). Besides, this model has a sensitivity of 90.00%, a specificity of 84.38% and its positive and negative predictive values are 93.51% and 77.14, respectively.

Regarding the model constructed by plasma biomarkers (neuroprostanes, isoprostanes, neurofurans, isofurans, 17-*epi*-17-F_{2t}-dihomo-IsoP, $PGF_{2\alpha}$), a negative correlation between PGF2α and isoprostanes and isofurans was observed, but age and gender did not correlate with biomarkers (Fig. 2c). Also, Fig. 2d shows a satisfactory discrimination between case and control groups. This model could diagnose AD or not-AD with an accuracy of AUC-ROC = 0.900 (0.845–0.956). The diagnosis indices for this model were sensitivity 72.5%, specificity 100%, negative predictive value 59.26% and positive predictive value 100%.

4. Discussion

The parameter MTA is commonly related to cerebrovascular dementias (Kalaria and Ihara, 2017). Previous works showed that this morphological alteration is associated with MCI and AD, showing higher damage grade in AD than in MCI patients, as well as a correlation with neuropsychological evaluation tests (e.g. MMSE, CDR) (Hsu et al., 2015). In this sense, some cut-off values for MTA to be used as AD diagnosis and MCI prognosis were established (Ferreira et al., 2015). In addition, MTA is related to cognitive impairment in patients with Dementia with Lewy Bodies (Tagawa et al., 2015). Medial temporal lobe atrophy evaluation contributes to a better diagnosis accuracy (Visser et al., 1999). Moreover, correlations between MTA and CSF biomarkers t-tau and p-tau for different variants of Early-Onset Alzheimer Disease (EOAD) were described (Granadillo et al., 2017). Nowadays, neuropsychological tests and CSF biomarkers are employed as AD diagnosis, these two parameters could be related to MTA, so the evaluation

Table 2
Concentrations of analytes in plasma samples from participants groups.

	Control (n = 32)	Case (n = 80)	P value
8-iso-15(R)-$PGF_{2\alpha}$	0.25 (0.20–0.35)	0.30 (0.23–0.49)	0.042*
PGE_2	0.06 (0.01–0.75)	0.09 (0.00–0.28)	0.693
2,3-dinor-$iPF_{2\alpha}$-III	0.00 (0.00–0.00)	0.00 (0.00–0.03)	0.950
8-iso-15-keto-PGE_2	0.06 (0.00–0.17)	0.13 (0.00–0.34)	0.425
8-iso-15-keto- $PGF_{2\alpha}$	0.25 (0.18–0.33)	0.26 (0.13–0.35)	0.754
8-iso-PGE_2	0.28 (0.15–1.98)	0.39 (0.18–0.78)	0.689
5-$iPF_{2\alpha}$-VI	0.94 (0.67–1.22)	0.71 (0.35–1.22)	0.123
8-iso-$PGF_{2\alpha}$	0.02 (0.01–0.03)	0.02 (0.01–0.03)	0.841
$PGF_{2\alpha}$	0.74 (0.60–0.94)	0.48 (0.25–0.78)	0.001*
4(RS)-F_{4t}-NeuroP	1.03 (0.71–1.24)	1.15 (0.96–1.33)	0.030*
1a,1b-dihomo-$PGF_{2\alpha}$	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.326
Neuroprostanes	0.29 (0.22–0.38)	0.83 (0.26–1.52)	0.001*
10-epi-10-F_{4t}-NeuroP	0.11 (0.07–0.18)	0.09 (0.03–0.18)	0.390
14(RS)-14-F_{4t}-NeuroP	0.90 (0.00–1.51)	0.80 (0.29–1.27)	0.930
Isoprostanes	0.22 (0.18–0.34)	0.32 (0.23–0.40)	0.006*
Ent-7(RS)-F_{2t}-dihomo-IsoP	0.08 (0.05–0.17)	0.13 (0.08–0.18)	0.145
17-F_{2t}-dihomo-IsoP	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.302
17-epi-17-F_{2t}-dihomo-IsoP	0.00 (0.00–0.00)	0.00 (0.00–0.03)	0.008*
7(RS)-10-epi–SC–Δ^{15}-11-dihomo-IsoF	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.150
7(RS)-ST-Δ^8-11-dihomo-IsoF	0.10 (0.01–0.25)	0.05 (0.01–0.19)	0.199
Neurofurans	0.18 (0.11–0.26)	0.18 (0.13–0.27)	0.762
Isofurans	0.09 (0.06–0.22)	0.10 (0.08–0.16)	0.399

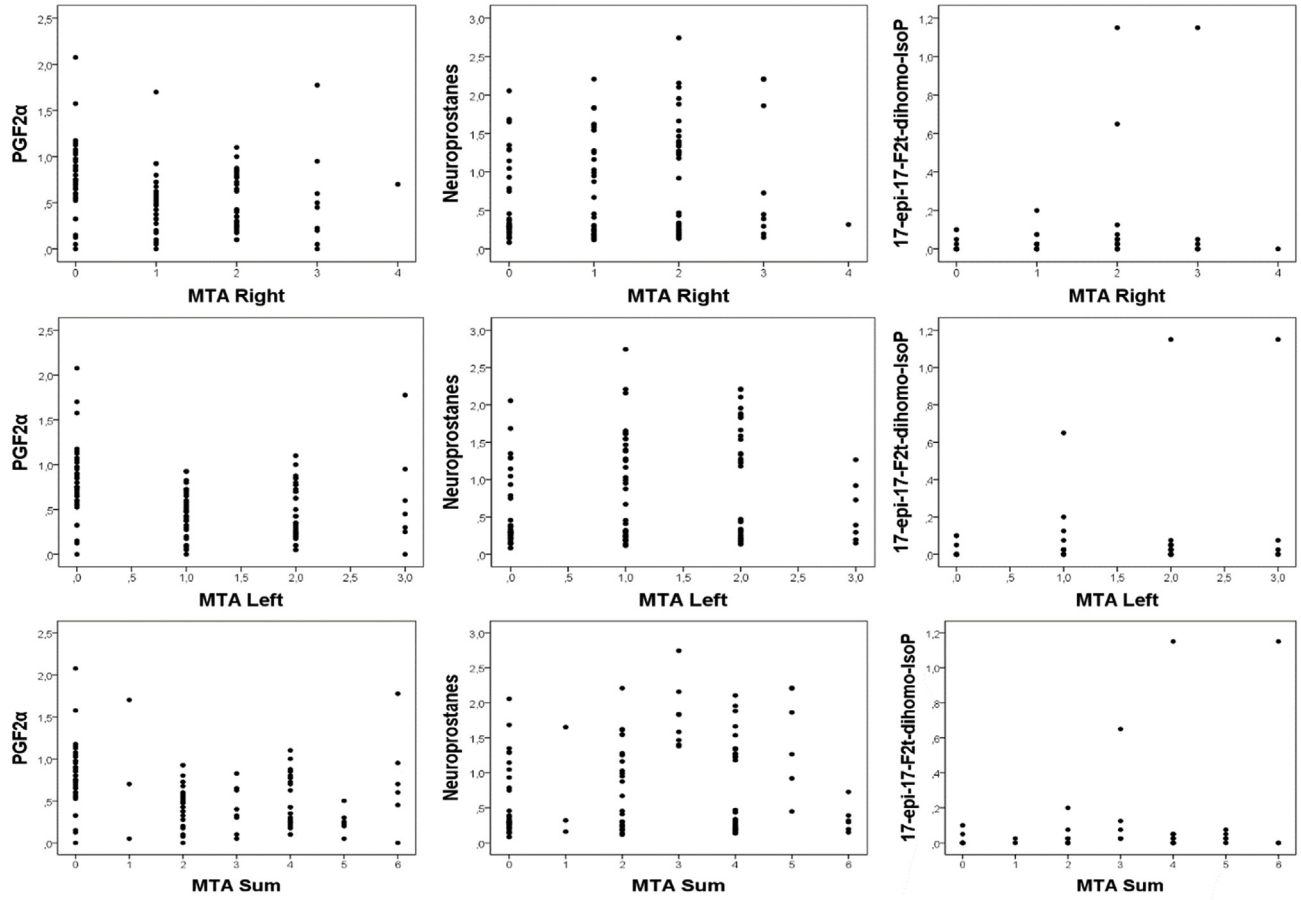

Fig. 1. Correlations between neuroimaging variables and plasma biomarkers levels.

of atrophy could be useful in AD diagnosis, as well as the lipid peroxidation study as a possible pathway implied in AD. Our results showed that a diagnosis model based only on this atrophy evaluation could diagnose AD with an accuracy of 0.929. It could avoid actual lumbar puncture used in AD diagnosis nowadays, as well as neuropsycological evaluations that require a considerable amount of time on part of specialized staff and is tiresome for patients. In this sense, other diagnosis models for AD based on neuroimaging techniques have been developed. Specifically, a model based on Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) was able to differentiated between AD, MCI and healthy control groups with accuracies between 0.75 and 0.95 (Suk et al., 2014). The model developed by Canu et al. (2017) was able to distinguish between EOAD and behavioral variant of frontotemporal dementia with an accuracy of 0.82 based on cortical thickness and DT (diffusion tensor) MRI measures (Canu et al., 2017). Our model shows better accuracy, but its specificity is required to be evaluated employing other dementias or neurodegenerative diseases. This model shows good diagnosis indices, especially its high specificity that could allow the application of this model as a preliminary screening test although it probably needs other tests to give a reliable diagnosis.

Regarding the evaluation of possible correlations between neuroimaging results (MTA) and different lipid peroxidation products in plasma samples form AD and healthy participants, the highest correlations were between brain MTA and neuroprostanes. Therefore, specific brain alterations could be measured in plasma samples by means of these lipid peroxidation products (Miller et al., 2014). As MTA scale is based mainly in grey matter atrophy, neuroprostanes could explain this alteration evaluation (Scheltens et al., 1992). In addition, neuroprostanes levels were statistically significant different between AD and healthy participants. Therefore, they are satisfactory AD biomarkers. In addition, the dihomo-isoprostanes could be obtained from brain white matter oxidation. The correlation found between MTA and these compounds could be explained as some white matter atrophy that occurs together with the grey matter alterations in medial temporal lobe mainly in the hipocampus from AD patients. We also analyzed correlations between our biomarkers and Fazekas, which is a scale based on brain white matter lesions and it is usually related to vascular pathologies. This scale is not AD specific but it could help to discard AD as a cause of vascular dementia (Fazekas et al., 1987). Punctuation for this scale showed statistically significant correlation with 17-F_{2t}-dihomo-IsoP that is a white matter lipid peroxidation product. So, this biomarker could be useful in the study of white matter lesions present in different neudegenerative diseases, not only in AD, and sometimes it could serve to discard AD diagnosis or to differentiate it from frontotemporal dementia whose symptoms could be confused (Elahi et al., 2017).

Regarding plasma biomarkers, neuroprostanes and neurofurans are derived from docosahexaenoic acid (DHA) oxidation, while isoprostanes and isofurans come from the arachidonic acid (AA) oxidation (Yen et al., 2015), and dihomo isoprostanes (e.g. 17-*epi*-17-F_{2t}-dihomo-IsoP) come from adrenic acid (AdA) oxidation (García-Flores et al., 2016). DHA is the major polyunsaturated fatty acid in the brain (Galano et al., 2013) so, the presence of neuroprostanes and neurofurans in different human biofluids is highly brain specific. For the quantification of these lipid peroxidation biomarkers in plasma samples, the analytical method was previously described (Peña-Bautista et al., 2018), and the developed model could distinguish between AD and healthy patients with an accuracy of 0.90. Therefore, it could reflect brain lipid peroxidation damage (neuroprostanes, neurofurans, 17-*epi*-17-F_{2t}-dihomo-

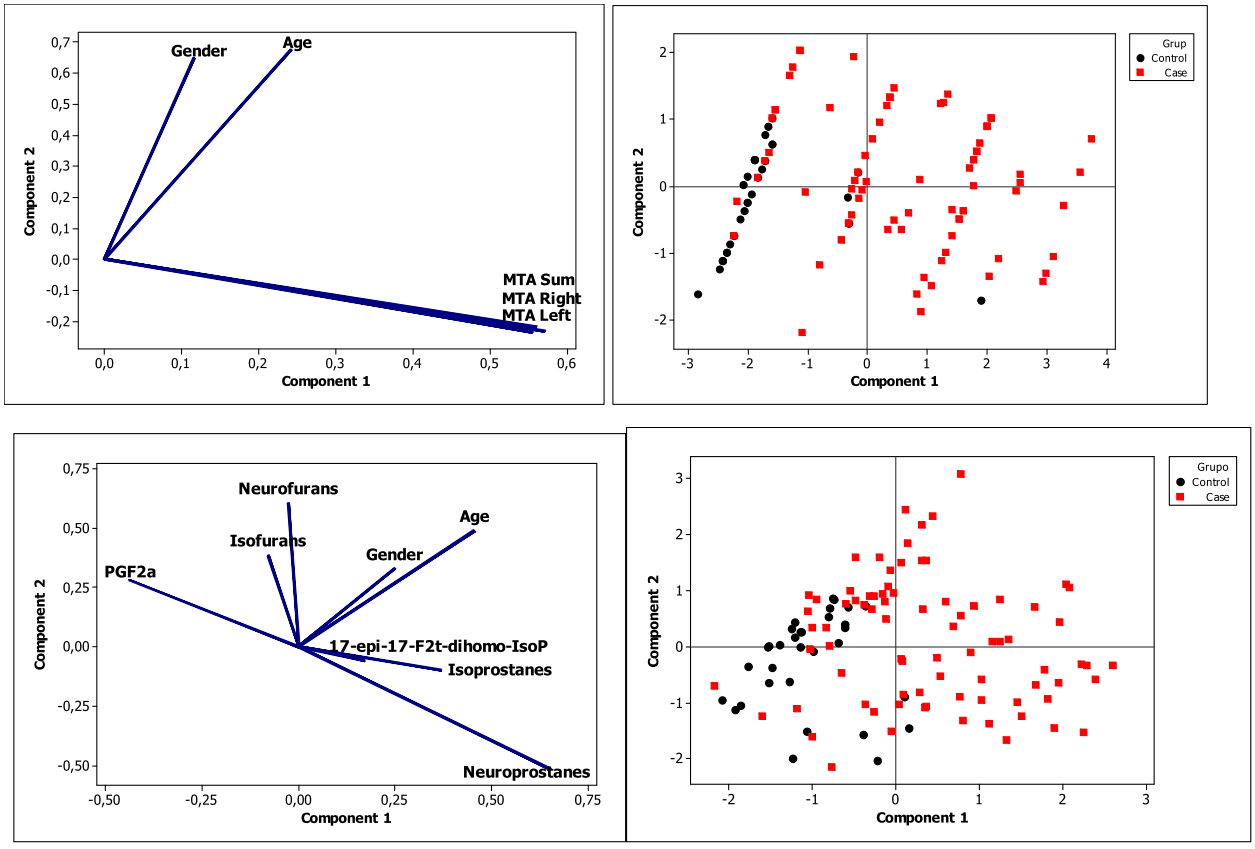

Fig. 2. PLS models. First, model based on neuroimaging techniques (a) loading graph and (b) score plot. Second, model based on plasma biomarkers (c) loading plot and (d) score plot.

IsoP), and oxidative stress at systemic level in AD patients. In fact, it was shown in previous works (Hatanaka et al., 2015) (Di Domenico et al., 2016). Also, the presence of a negative correlation between $PGF_{2\alpha}$ and MTA, and its capacity to discriminate between AD and control groups ($p = 0.001$) are remarkable. This analyte is an inflammatory mediator and it is derived from arachidonic acid oxidation by an enzymatic pathway (Vane et al., 1998). Previous studies showed that inflammation is related to AD progression (Calsolaro and Edison, 2016), and inhibition of cyclooxygenases that are implied in prostaglandin pathway in AD models, showed beneficial effects. So, probably in very early stages of the disease these mechanisms try to avoid the disease progression (Johansson et al., 2015). In addition, it is known that in neurodegenerative diseases the brain blood barrier (BBB) is altered (Janelidze et al., 2017). Specifically in AD, previous works showed an increase on BBB permeability (Algotsson and Winblad, 2007), allowing that different lipid peroxidation products generated in brain could pass through the BBB, and being found at peripheral level. For this reason, we constructed a model based on plasma biomarkers levels that could reflect brain MTA including damage to white matter, grey matter and also inflammatory mediators. That model shows really satisfactory diagnosis indices. Its specificity of 100% is especially remarkable. In our study, all patients diagnosed as positive with our model were AD patients. By contrast, its weak point is the sensitivity (72.5%). For that reason, the new model could serve as a screening test. Only when the test result is negative, patients will have to undergo additional tests to confirm the diagnosis. It would improve the diagnosis based on only image tests because biomarkers reflecting specific brain atrophy in AD patients would constitute an integrative vision of oxidative status (Pohanka, 2014). In any case, more studies are required to confirm this diagnosis capacity, and other dementias or neurodegenerative diseases have to be included in the study to evaluate the model specificity.

5. Conclusion

Correlation between plasma neuroprostanes and dihomoisoprostanes with neuroimaging data could indicate that the neurodegeneration occurred in different brain areas is related to oxidative stress damage and brain lipid peroxidation. Lipid peroxidation biomarkers could reflect brain damage that accompanied neurodegenerative diseases. However, their specificity should be studied comparing the results with other neurodegenerative and brain pathologies. AD diagnosis model based on lipid peroxidation biomarkers shows similar accuracy as the neuroimaging model, and it reflects the implication of this pathway in the pathology since its early stages. The model based on lipid peroxidation biomarkers (neuroprostanes, neurofurans, isoprostanes, isofurans, 17-*epi*-17-F_{2t}-dihomo-IsoP, $PGF_{2\alpha}$) could be used as a screening test for AD diagnosis avoiding in many cases invasive and expensive diagnosis techniques.

Conflicts of interest

The authors report no conflict of interest.

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