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Review

Free radicals in Alzheimer's disease: Lipid peroxidation biomarkers

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ABSTRACT

Alzheimer's disease (AD), the most common form of dementia, has tremendous social and economic impact worldwide. Research has shown an association between pathologic development of AD and increased free-radical production. As such, the role of peroxidation in brain lipid damage and AD progression has received special attention. Previous studies on lipid peroxidation have improved our understanding of the unique pathophysiologic processes involved in AD. These studies have also served to identify potentially new biomarkers including lipid peroxidation metabolites for diagnosis, prognosis and therapy. Unfortunately, these putative markers have generated controversial results and further research, especially early stage AD, is clearly warranted. The aim of this paper is to review the usefulness of lipid peroxidation biomarkers in AD diagnosis and prognosis as well as monitoring disease development and therapeutic treatment thereof.

1. Introduction

1.1. Alzheimer's disease

Alzheimer's Disease (AD) is the most common cause of dementia worldwide. It is clinically characterized by progressive memory loss, and it is the most common form of pathologic neurodegeneration [1]. In general, AD incidence increases dramatically after 65 years old, and the number of AD patients is expected to increase considerably in the coming years [1,2]. In this sense, AD would have a great socio-economic impact [3]. Regarding AD physiopathology, it is characterized by two histological traces in brain: β-amyloid peptide forming senile plaques as extracellular deposits; and hyperphosphorylated tau protein forming neurofibrillary tangles as intracellular deposits [4]. Many risk factors have been associated with AD development. Genetic factors are some of them, but most of the AD cases are sporadic, and < 1% have a specific genetic cause [5]. Clinical evolution of AD can be divided in three phases: i) Preclinical AD, in which individuals conserve cognitive capacity but different biomarkers could be altered; ii) Mild cognitive impairment (MCI), when affected individuals show the first symptoms of cognitive impairment, the most common of which being episodic memory loss; iii) Dementia, when cognitive impairment affects the ability to carry out daily activities in an independent way, and individuals suffer from behaviour changes [6].

2. Free radicals in Alzheimer's disease

Free radicals chemistry is attracting attention because of its relationship with human diseases. Specifically, an excess of free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), are generated under pathological AD conditions [7], triggering an imbalance between free radical production and antioxidants mechanisms, known as oxidative stress condition.

Oxidative stress has been related to neurodegenerative pathologies and aging, so it could also play a fundamental role in the physiopathological mechanisms involved in AD [8]. Several studies showed that oxidative stress was mainly related to some brain changes [9,10], but it could also be associated with damage at systemic level (e.g. erythrocyte membrane stability and lymphocytes death susceptibility) [11,12]. In this sense, the evaluation of these changes in biofluids

Abbreviations: AD, Alzheimer's disease; CSF, Cerebrospinal fluid; DM, Diabetes Mellitus; DrD, Diabetes related dementia; EIA, Enzyme immunoassay; ELISA, Enzyme-linked immunosorbent assay; FLP, Fluorescent lipofuscin-like pigments; GC, Gas Chromatography; aMCI, Amnestic Mild Cognitive Impairment; MCI, Mild cognitive impairment; MDA, Malondialdehyde; 4-HNE, 4-hydroxy-2-nonenal; HPLC, High Performance Liquid Chromatography; HPNCI, High AD-like Pathology no Cognitive Impairment; α-LA, alpha Lipoic Acid; LDL, Low density lipoprotein; LOAD, Late onset Alzheimer's disease; LPH, Lipid Hydroperoxides; LPNCI, Low AD-like Pathology no Cognitive Impairment; MS, Mass spectrometry; NIA-AA, National Institute on Aging and Alzheimer's Association; POVPC, 1-palmitoyl-2-(5′-oxo-valeroyl)-sn-glycero-3-phosphocholine; PPAR, Peroxisome proliferator-activated receptor; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; SIVD, Subcortical ischemic vascular disease; TBARS, Thiobarbituric acid reactive substances; UPLC, Ultra-performance liquid chromatography

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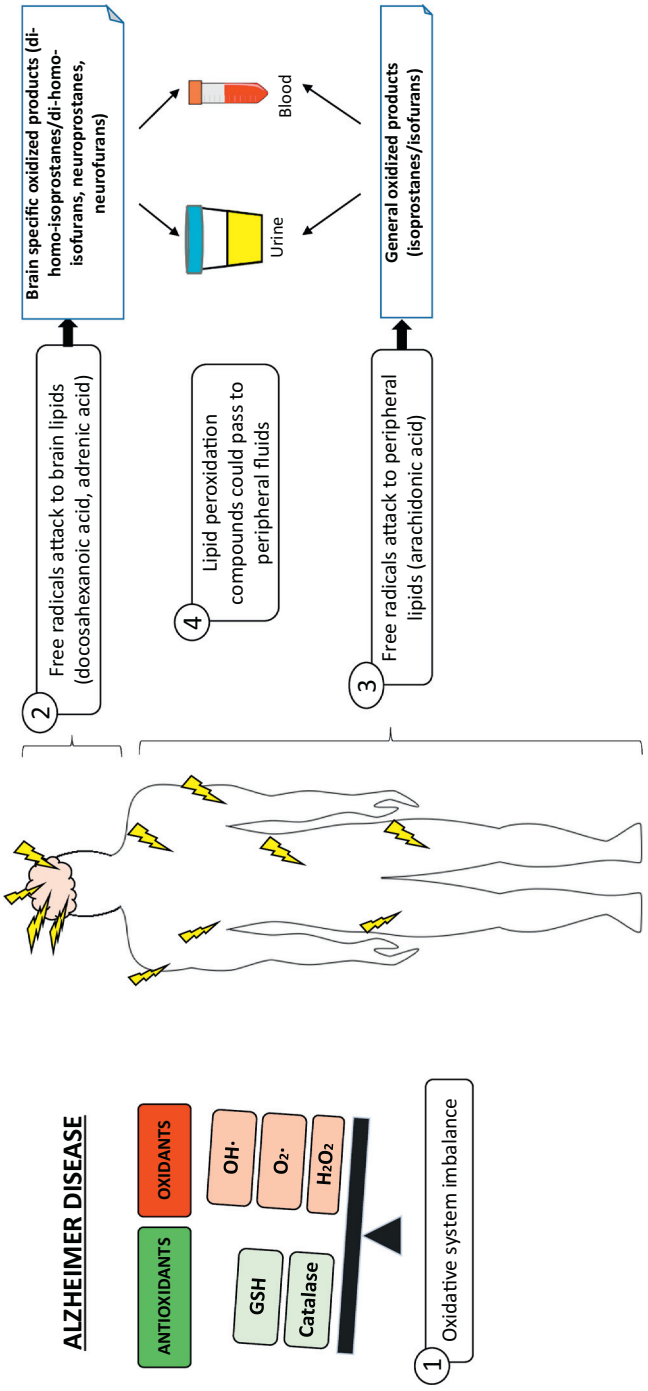

Fig. 1. Scheme representing the Central nervous System and peripheral lipid peroxidation associated to free radicals' production and oxidative stress triggered in Alzheimer disease.

would allow clarifying some issues about early diagnosis [13].

Of note, oxidative stress was found to be highly related to β-amyloid aggregation [14], but also β-amyloid plaques contributed to free radicals' generation, and oxidative stress [15]. According to this, high plasma levels of different oxidative stress biomarkers were found in MCI and Late Onset Alzheimer's disease (LOAD) [16]. In addition, a proteomic study showed that the higher risk for Down syndrome patients of suffering from AD could be explained by their higher susceptibility to oxidative stress damage accumulation [17].

3. Lipid peroxidation in Alzheimer's disease

Oxidative stress causes damage to biomolecules (proteins, lipid, DNA…) forming several oxidized molecules (carbonyls, peroxides, strand breaks…). The oxidative damage to lipids by ROS results in the formation of lipid peroxidation products, as depicted in Fig. 1. These lipid peroxidation products can be classified depending on the modified lipid. Thus, isoprostanes/isofurans are produced from arachidonic acid oxidation (all tissues), neuroprostanes/neurofurans from docosahexanoic acid oxidation (brain grey matter), and di-homo-isoprostanes/di-homo-isofurans from adrenic acid oxidation (brain white matter) [18,19]. Therefore, lipid peroxidation seems to play an important role in AD since the brain has a high lipid content and a high oxygen consumption [20].

Regarding the relationship between lipid peroxidation and AD, histological studies showed a co-localization of lipid peroxidation metabolites and β-amyloid plaques in the brain [21]. Similarly, fatty acids (C22:0, C24:0 and C26:0) that were found in AD brain lesions produced a neurotoxic effect in cell culture increasing oxidative stress [22]. Another study found decreased levels of PTEN-induced putative kinase 1 (PINK1) and PPARγ coactivator-1 (PPARGC1A), proteins involved in mitochondrial fatty acid oxidation [23]. Also, the alteration of some enzymatic activities (paraoxonase-1, platelet activating factor acetylhydrolase) showed a relationship with oxidized low-density lipoprotein (LDL) levels in AD [24].

3.1. Lipid peroxidation biomarkers for Alzheimer's disease diagnosis

Lipid peroxidation metabolites are highly related to AD development; therefore, they have been studied as potential disease biomarkers. For AD diagnosis, different studies evaluated some lipid peroxidation products (e.g. isoprostanes, malondialdehyde (MDA), thiobarbituric acid-reactive substances (TBARS), and fluorescent lipofuscin-like pigments (LPF)) in different human samples. As we can see in Table 1, the most used biofluids were blood (plasma, serum) and urine, and the most determined lipid peroxidation by-products were MDA and isoprostanes. Regarding groups of participants, they were mainly MCI, AD and healthy participants. Most studies involve groups of participants diagnosed as probable AD [25,26], or MCI subgroups (stable, converted to AD…) [27,28]. But most of these studies do not use National Institute on Aging and Alzheimer's Association (NIA-AA) research diagnostic criteria, with the consequent potential confounding results. On the other hand, there are few works that expanded their studies to other neurodegenerative diseases [29,30], such as vascular dementia [31–33], diabetes related dementia (DrD) [34], or preclinical AD [35].

Among the studies that analysed urine samples, Rubio-Perez et al. did not find any difference between AD patients and control groups [36], while Hatanaka et al. described higher values of 8-isoprostane in diabetes-dementia (DrD) than in AD-dementia [34]. In addition, high 8-isoprostane levels were found to be related to frailty in AD patients [37]. Moreover, urine isoprostanes levels were determined to evaluate different antioxidant treatments, showing no significantly different levels between the patients with treatment (omega-3 fatty acids, α-LA) and without treatment [38,39].

Regarding studies conducted with blood samples, MDA was the most evaluated biomarker. In general, it showed higher serum levels in AD patients than in healthy participants [39], but MDA levels from erythrocytes in AD patients did not differ from those of vascular dementia patients [32]. Thus it could not be considered a specific biomarker of AD. Also, MDA serum levels were reduced with vitamin B supplementation, but this treatment was not able to restore MDA levels to those found in healthy participants [40]. In addition, MDA levels did not show any correlation with cognitive tests, although cognitive alteration could be a late finding compared with biologic changes [29]. In plasma samples studies, MDA showed higher levels in MCI patients than in healthy participants [41], and higher values were found in MCI converted to AD cases comparing with stable MCI [27]. However, Gubandru et al. did not find any differences between AD and healthy controls [42]. Secondly, evaluation of isoprostanes (e.g. 8-isoPGF$_{2\alpha}$) in blood samples as potential biomarkers of AD was carried out. In general, higher levels of isoprostanes were found in AD patients than in healthy subjects [31,43]. Among other blood biomarkers, plasmatic levels of oxidized LDL and FLP showed higher levels in AD than in healthy participants [24], while no significant differences were found in TBARS levels between healthy participants and probably AD cases [25]. Also, FLPs were determined in plasma and erythrocytes, showing an increase in AD and MCI groups compared to healthy control group [44,45]. In serum samples, hydroperoxides and POVPC levels were different between AD and control groups showing higher levels in AD [43,16], while oxidized LDL levels were similar between AD patients and healthy participants [36]. Regarding 4-HNE biomarker, high variability was observed, showing no difference in serum levels between AD and control groups [33], while other studies found higher levels in lymphocyte mitochondria from MCI patients compared to healthy participants [46]

Other studies used invasive samples, such as brain tissue and cerebrospinal fluid (CSF) samples, since this type of sample could show the oxidative damage in AD brain better. In this sense, different oxidized lipids co-localized with senile plaques [21], oxysterols levels correlated with AD progression [47], and 4-HNE showed differences among patients with different cognitive impairment degrees [35,21,47]. In addition, isoprostanes were determined in CSF samples, but no correlation was observed with CSF standard biomarkers (β-amyloid, tau, p-tau) levels [48], and neither was any difference observed between healthy and probable AD groups of participants [26].

Regarding the analytical techniques, the most used ones were immunoassays and colorimetric assays, and they were applied to the determination of several compounds, such as isoprostanes [31,33,34,36,37,43], TBARS [25], MDA [42,49], oxidized LDL [36,24] and hydroperoxides [16]. However, they showed low sensitivity and selectivity. Western-blot and microscopy techniques were also used for tissue or cell samples analysis, specifically to detect 4-HNE [35,46] and oxidized lipids [21]. Nevertheless, few studies used chromatographic and mass spectrometry techniques, and they were mainly used to determine MDA [27,29,40], isoprostanes [39,48] and oxysterols [47], showing the advantages of low limits of detection, high sensitivity, selectivity (simultaneous quantification of different isomers) and robustness.

3.2. Lipid peroxidation for Alzheimer's disease treatment monitoring

Some antioxidant products have been tested as potential AD treatments, such as resveratrol derivatives [50], selenium-containing clioquinol derivatives [51], and resveratrol-clioquinol combination. In general, these aforementioned treatments showed some results in β-amyloid aggregates reduction [52]. In addition, other treatments against oxidative stress showed beneficial effects, as chiral metallohelical complexes that also inhibited β-amyloid aggregates formation [53], and a heptapeptide that reduced the formation of ROS [54]. Moreover, hesperidin a flavonoid postulated as potential AD treatment led to an increase in antioxidant levels. It could improve cognitive

Table 1
Lipid peroxidation biomarkers determined in biological samples from AD patients.

Reference	Participants	Biomarker	Sample	Analytical technique	Results
[34]	AD (n = 31) AD + DM (n = 58) DrD (n = 35)	8-isoprostane	Urine	EIA	AD < DrD* AD + DM < DrD*
[36]	Healthy participants (n = 52) AD (n = 48)	Isoprostanes Oxidized LDL	Urine Serum	ELISA ELISA	Not differences between groups
[37]	Non-frail AD (n = 44) Pre-frail AD (n = 62) Frail AD (n = 34)	8-isoprostane	Urine	EIA	Non-frail AD < Pre-frail AD* Non-frail AD < Frail AD*
[38]	AD + treatment (n = 17) AD + placebo (n = 20)	8-isoprostane	Urine	RIA	AD + placebo > AD treatment
[39]	AD + placebo (n = 13) AD + ω-3 (n = 13) AD + (ω-3 + LA) (n = 13)	Isoprostanes	Urine	GC–MS	Not differences between groups after the treatment
[63]	Healthy participants (n = 5) MCI-AD (n = 5) Mild dementia-AD (n = 8)	Isoprostanes, neuroprostanes, dihomo-isoprostanes	Urine	UPLC-MS/MS	Some of the compounds (NeuroP, IsoP, IsoF and PGE2) showed statistically significant differences among groups.
[27]	Healthy participants (n = 62) aMCI stable (n = 118) aMCI converted to AD (n = 62) AD (n = 84)	MDA	Plasma	HPLC-Fluorescence	aMCI converted > aMCI stable*
[29]	Patients with probably neurodegenerative diseases (n = 97) AD (n = 35)	MDA	Blood	HPLC-MS	MDA blood levels do not correlated with different cognitive tests
[32]	Healthy participants (n = 40) AD (n = 30) Vascular Dementia (n = 35)	MDA	Blood erythrocyte	Spectrophotometry	Healthy participants < (AD, Vascular Dementia)*
[40]	Healthy participants (n = 15) AD/MCI (n = 16) AD/MCI + Vitamin B (n = 17)	MDA	Serum	HPLC-Fluorescence	Healthy participants < AD/MCI + Vitamin B < AD/MCI
[41]	Healthy participants (n = 138) MCI (n = 138)	MDA	Plasma	Commercial kit	Healthy participants < MCI*
[42]	Healthy participants (n = 10) AD (n = 21)	MDA	Plasma	Colorimetric assay	Not differences between groups
[49]	Healthy participants (n = 15) MCI (n = 15) AD (n = 15)	MDA	Serum	Colorimetric Assay	Healthy participants < MCI* Healthy participants < AD*
[28]	Healthy participants (n = 26) MCI-AD (n = 68)	Isoprostanes, neuroprostanes, dihomo-isoprostanes	Plasma	UPLC-MS/MS	Some isoprostanes, neuroprostanes and dihomoisoprostanes showed higher levels in MCI-AD. A multivariable diagnosis model based on these compounds achieved an AUC-ROC of 0.883
[33]	Minimal SIVD (n = 20) Extensive SIVD (n = 28) AD with minimal SIVD (n = 13) AD with Extensive SIVD (n = 12)	8-Isoprostane LPH 4-HNE	Serum	Colorimetric assay ELISA ELISA	8-Isoprostane, LPH, and 4-HNE are not good to distinguish patients with AD.
[43]	Healthy participants (n = 16) AD (n = 21)	8-Isoprostane POVPC	Serum	ESI-MS ELISA	8-Isoprostane: AD > Healthy participants POVPC: AD > Healthy participants*
[64]	Healthy participants (n = 20) MCI (n = 21) AD (n = 22)	8-isoprostane	Plasma	EIA	Healthy < MCI < AD Healthy < AD*
[25]	Healthy participants (n = 42) Probably AD (n = 23)	TBARS	Plasma	Colorimetric assay	Not differences between groups
[45]	AD (n = 19) aMCI (n = 27) Healthy participants (n = 16)	FLPs	Blood (erythrocytes)	Fluorescence spectroscopy	(AD + aMCI) > healthy participants
	AD (n = 11) aMCI (n = 17) healthy participants (n = 16)	FLPs	Plasma		
[16]	Healthy participants (n = 118) MCI (n = 111) LOAD (n = 105)	Hydroperoxides	Serum	Colorimetric assay	MCI > Healthy participants*
[46]	Healthy participants (n = 5) MCI (n = 5) AD (n = 5)	4-HNE	Mitochondria from blood	Western blot	Healthy control < MCI*
[30]	Neurodegenerative disease patients (n = 30)	Isoprostanes, neuroprostanes, dihomo-isoprostanes	Saliva	UPLC-MS/MS	The analytical method showed good precision and accuracy

(*continued on next page*)

Table 1 (*continued*)

Reference	Participants	Biomarker	Sample	Analytical technique	Results
[26]	Healthy participants (n = 83) MCI (n = 164) Probable AD (n = 101)	Isoprostanes (Ipf2α-III and 8,12, isoIpf2α-VI F2-isoprostane)	CSF	HPLC-atmospheric pressure chemical ionization-MS	No differences between groups
[48]	Healthy participants between 21 and 100 years old (n = 320)	Isoprostanes	CSF	GC–MS	CSF Isoprostanes do not correlate with CSF β-amyloid and Tau
[35]	LPNCI (n = 22) HPNCI (n = 15) aMCI (n = 15)	4-HNE	Brain tissue	Western-blot	LPNCI < (HPNCI and MCI)*
[21]	AD	Oxidized lipids	Brain tissue	Microscopy	Co-localization between lipid oxidation products and senile plaques
[47]	Healthy participants (n = 4) AD (n = 13)	Oxysterols	Brain	GC–MS	Correlation between oxysterols levels and AD pathology progression

* $p < 0.05$.

status despite the fact that β-amyloid aggregates seemed not to be reduced [55]. Also, oligonol was tested, resulting in a reduction of oxidative stress [56]. In the same sense, some sulphonamides showed effects on free radicals' reduction [57]. Also, silencing of some genes (e.g. APP, Tau, VDAC1, GSK-3β) was tested as potential AD treatment since it could reduce the oxidative stress levels [58,59]. Most of these AD treatments showed promising results in cell culture or animal models, but they were not tested in humans [55,60-62].

Regarding lipid peroxidation, omega-3 fatty acids supplementation was tested in humans. Its effect was measured by means of isoprostanes and no potentially beneficial effects were observed for this proposed treatment [39,38]. From previous findings related to lipid peroxidation and AD development, we developed a promising diagnosis model based on the plasma levels of some lipid peroxidation compounds [28]. For this approach, an analytical method based on liquid chromatography coupled with mass spectrometry was used. It had the advantages of high sensitivity and selectivity in comparison to previous studies using immunoassays and colorimetric assays. In addition, the corresponding analytical methods to determine a set of lipid peroxidation compounds in urine and saliva samples were developed by our research group [30,63]. However, further clinical work is required to validate the potential diagnosis model, and to develop a treatment monitoring system in order to restore the normal lipid peroxidation levels.

4. Conclusions

Recent research has focused on the link between free radicals and the formation of β-amyloid aggregates in AD development. In this sense, there is a large controversy regarding the consideration of free radicals as an AD cause or consequence. In any case, it seems clear that oxidative stress and, specifically, lipid peroxidation, are molecular pathways involved in early AD development. Therefore, this relationship could be useful for AD diagnosis and treatment monitoring.

As AD potential biomarkers, some lipid peroxidation metabolites have been studied in different human samples showing promising but varied results. However, further research is needed in the early and well-defined AD stages, involving cases defined according to NIA-AA definition of MCI-AD cases, with validated, sensitive, specific and reproducible analytical techniques in order to establish lipid peroxidation as a reliable target pathway in AD.

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Conflict of interest

The authors report no conflict of interest.

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